HYPOPARATHYROIDISM

CHI Formulary Development Project

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

1,25(OH)2D	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
ADH	Autosomal Dominant Hypocalcemia
AIRE	Autoimmune Regulator
APECED	Autoimmune Polyendocrinopathy – Candidiasis – Ectodermal Dystrophy Syndrome
BAETS	British Association of Endocrine and Thyroid Surgeons
BID	Twice a Day
BMD	Bone Mineral Density
BUN	Blood Urea Nitrogen
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CT	Computed Tomography
DXA	Dual-Energy X-ray Absorptiometry
eGFR	Estimated Glomerular Filtration Rate
EKG	Electrocardiogram
FDA	U.S. Food and Drug Administration
GFR	Glomerular Filtration Rate
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
HypoPT	Hypoparathyroidism
IDF	CHI Drug Formulary
IOPTH	Intraoperative PTH
IQWIG	Institute for Quality and Efficiency in Healthcare
IV	Intravenous
N/A	Not Available/Not Applicable
NICE	National Institute for Health and Care Excellence
PA	Prior Authorization
PBAC	Pharmaceutical Benefits Advisory Committee
PO	Taken by Mouth
PTH	Parathyroid hormone
PTHrP	Parathyroid Hormone-Related Protein
rhPTH	Recombinant Human Parathyroid Hormone
SFDA	Saudi Food and Drug Authority
TID	Three Times a Day

Executive Summary

Hypoparathyroidism is a rare condition characterized by insufficient production of parathyroid hormone (PTH), which is crucial for regulating calcium and phosphorus levels in the body. Low PTH leads to low calcium and high phosphorus levels in the blood[1]. This condition is often caused by factors such as neck surgery, autoimmune diseases, hereditary factors, or low magnesium levels. Symptoms of hypoparathyroidism include tingling or burning sensations, muscle cramps, twitching, weakness, and other issues like painful menstrual periods, hair loss, dry skin, brittle nails, and mood changes[1].

Complications can be reversible, including spasms, kidney problems, and heart arrhythmias, but irreversible complications can also occur and include bone abnormalities, developmental issues in children, brain calcium deposits, cataracts, and dental problems. While there's no specific way to prevent hypoparathyroidism, people undergoing thyroid or neck surgery should discuss the risk of damage to their parathyroid glands with their surgeon and may need calcium and vitamin D supplements before the procedure. Parathyroid auto-transplantation may also be an option to reduce the risk of postoperative hypoparathyroidism. Monitoring symptoms and early treatment are essential if you've had thyroid or neck surgery to minimize the impact of the disorder[1].

The prevalence of hypoparathyroidism can vary by region, but it is estimated to occur in approximately 25 to 37 cases per 100,000 individuals in the United States[2]. Prevalence rates in other countries may be similar or slightly different[2]. A retrospective cohort analysis in Taif city between 2015 and 2019 studied adult patients who underwent total thyroidectomy[3]. The study found a 10.3% incidence of hypoparathyroidism, with a higher prevalence in females (12.1%) than males (3.2%)[3]. Patients with two or three parathyroid glands showed a higher prevalence of hypoparathyroidism in permanent histological sections (33.3% and 25.5%, respectively)[3]. The analysis did not identify a single independent risk factor for hypoparathyroidism[3].

This report compiles all clinical and economic evidence related to Hypoparathyroidism according to the relevant sources. The ultimate objective of issuing Hypoparathyroidism guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to Hypoparathyroidism patients in Saudi Arabia**.

The main focus of the review was on North American and European and other international guidelines issued within the last five years. To elaborate, North American guidelines detailed the management of Hypoparathyroidism in both adults and patients transitioning from pediatric to adult care. It also discusses

parathyroid hormone replacement therapy. Furthermore, joint European and International guidelines elaborated on the use of the newly approved and SFDA registered drug; Natpara® (parathyroid hormone) for the management of hypoparathyroidism. The guidelines also emphasize safety considerations and potential drug-drug interactions when a patient is subjected to therapy. In addition, a recent systematic review and meta-analysis was included; thereby providing an in-depth understanding of the different hypoparathyroidism drug therapies and their placement in pharmacological management.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in hypoparathyroidism were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

The management of hypoparathyroidism involves a **multidisciplinary approach**. **Drug therapy is an integral component for the management of hypoparathyroidism.** The major goal for the hypoparathyroidism pharmacological approach is to correct the wide spectrum of associated clinical alterations. The standard pharmacological interventions for hypoparathyroidism include the administration of calcium and active vitamin D supplements. Newer agents for the treatment of hypoparathyroidism include the parathyroid hormone analog teriparatide. In 2015, a new drug Natpara® (parathyroid hormone) was approved by the FDA for the treatment of Hypoparathyroidism. Natpara® (parathyroid hormone) is not registered by the SFDA.

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of AGHD.

Major recommendations for suggested **SFDA-registered** drug therapies are summarized in table 1.

Table 1. SFDA-Registered Drug Therapies for the Management of Hypoparathyroidism

Medication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Calcium	Standard practice[4]	Low quality of evidence[4]	N/A
Vitamin D	Standard practice[4]	Low quality of evidence[4]	N/A
Magnesium	Standard practice[4]	Low quality of evidence[4]	N/A
Teriparatide	Not routine use[5]	Very low quality of evidence[5]	N/A
Hydrochlorothiazide	To reduce urinary calcium excretion/ for persistent hypercalciuria despite calcium and vitamin D supplementation[4]	Low quality of evidence[4]	N/A
Sevelamer	If need to control hyperphosphatemia[4]	N/A	N/A

Major recommendations for suggested **non-SFDA-registered** drug therapies are summarized in table 2.

Table 2. Non-SFDA-Registered Drug Therapies for the Management of Hypoparathyroidism

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation
Natpara® (parathyroid hormone) (PTH 1-84)	Hormone replacement therapy, Hypoparathyroidism	Alternative/ Step Therapy after calcium and Vitamin D Supplementation	Low quality of evidence[4]

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, there are no available Saudi guidelines issued for the management of hypoparathyroidism.

1.2 North American Guidelines

1.2.1 American Thyroid Association Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults (2018)

The American Thyroid Association (ATA) issued in 2018 a statement aiming to provide an overview on the diagnosis, prevention, and treatment of postoperative hypoparathyroidism. Evidence levels and grades of recommendation were not outlined[6].

I. Symptoms and signs

Hypocalcemia effects: Reduced nerve and muscle cell depolarization threshold, leading to neuromuscular excitability and cardiac electrical instability.

Early symptoms of hypocalcemia:

- Paresthesias (numbness and tingling) in the perioral region and fingertips.
- Muscle stiffness, cramps, and spasms.
- Neuropsychiatric symptoms like confusion, anger, depression, lightheadedness, and irritability.

Severe symptoms of hypocalcemia: Laryngospasm due to sustained muscle contraction and seizures due to increased neural excitability.

Signs of hypocalcemia:

- Positive Chvostek sign (facial muscle twitching when tapping the preauricular region).
- Positive Trousseau sign (wrist, thumb, and finger flexion upon brachial artery occlusion).
- Cardiovascular signs include QT interval prolongation and torsades de pointes.

II. Risk factors

- Central neck operation (simultaneous or staged bilateral).
- Prior partial thyroid operation.
- Limited thyroidectomy may reduce risk, but the effectiveness is not well-studied.
- Parathyroid auto-transplantation can increase temporary risk but may reduce permanent risk.

The following table provides a summary of the risk factors for permanent hypoPT following thyroid-related operations:

Table 3. Risk Factors for Permanent Hypoparathyroidism Following Thyroid-Related Operations

Risk Factors for Permanent Hypoparathyroidism (HypoPT) Following Thyroid-Related Operations
• Bilateral (simultaneous or sequential) thyroid procedures • Autoimmune thyroid disease (Graves' disease, chronic lymphocytic thyroiditis) • Central neck dissection—prophylactic or therapeutic • Substernal goiter • Low-volume thyroid surgeon • Prior gastric bypass or other malabsorptive state • Simultaneous thyroidectomy and parathyroidectomy • Prior central neck surgery

III. Preoperative vitamin D deficiency

- Low preoperative calcium may increase the risk of hypoPT, and it may be appropriate to initiate scheduled oral calcium supplementation preoperatively.
- If the baseline calcium level is elevated, then the PTH level should be measured in order to evaluate occult primary hyperparathyroidism, which could be definitively treated during thyroidectomy.
- Elevated preoperative PTH is commonly due to secondary hyperparathyroidism from vitamin D deficiency.
- Correction of vitamin D deficiency before surgery is advisable, and supplementation may be helpful to patients with hypoPT, assuming no underlying malabsorptive condition is present.

- FDA-approved regimen is 50,000 IU of vitamin D3 (cholecalciferol) weekly or 6000 IU daily for eight weeks followed by maintenance dose. More aggressive regimens and other vitamin D supplements are available, but their utilization should be considered off-label.

IV. Surgical techniques and tools

Preserving all four parathyroid glands is crucial.

Parathyroid Identification: Parathyroid glands are small and may resemble nearby tissues; special techniques like fluorescence imaging help.

Capsular Dissection: Gentle dissection around the thyroid helps preserve parathyroid blood supply.

Energy Devices: Careful use of energy devices to avoid thermal injury to parathyroid glands.

Number of Parathyroids Visualized: The number visualized during surgery can impact hypocalcemia risk. It is not essential to visualize all four glands to reduce the incidence of postoperative hypocalcemia.

Central Lymph Node Dissection: Increases the risk, especially for inferior parathyroid glands.

V. Parathyroid auto-transplantation (PA)

Purpose: Maximize retained functional parathyroid tissue.

Assessment: Glands checked for devascularization; PA performed if needed.

Technique: To achieve PA, the initial step involves preserving the removed parathyroid in cold saline, all the while sending a small portion of the parathyroid tissue for immediate frozen section confirmation. Subsequently, the parathyroid gland is finely chopped into 1 mm pieces, which are then transplanted back into the body through direct implantation or injection into specific areas, such as intramuscular or subcutaneous pockets, located within the sternocleidomastoid muscle or other suitable locations. The primary goal of this procedure, known as PA, is to minimize the likelihood of enduring hypoparathyroidism.

Effect on HypoPT: May increase temporary risk but reduce permanent risk.

VI. Biochemical testing: perioperative calcium and PTH

Predicting transient hypoPT:

- Serial calcium measurements post-thyroidectomy.
- Intraoperative PTH (IOPTH) measurements are helpful.

- IOPTH < 15 pg/mL predicts impending hypocalcemia.

Determining discharge: IOPTH ≥15 pg/mL at ≥20 minutes post-thyroidectomy may obviate the need for intensive calcium monitoring.

Transient vs. permanent hypoPT: Uncertain; several parameters may be relevant but require further study.

VII. Postoperative management

- The postoperative management of hypoPT aims to prevent hypocalcemia symptoms and complications.
- Acute hypocalcemia can occur after thyroid surgery, often after the patient is discharged, so anticipating and educating patients about it is essential.
- Monitoring serum calcium levels, vitamin D, and magnesium is crucial in managing hypoPT.

Prophylactic postoperative management

- Prophylactic management often involves prescribing oral calcium and calcitriol without testing PTH or calcium levels, which can help reduce postoperative hypocalcemia.
- Oral calcium carbonate is given as 500–625 mg to 1000–1250 mg two to three times a day.
- Adding calcitriol (1,25-(OH)2-D3), usually in a dose of 0.5–1.0 lg per day increases the effectiveness of oral calcium.

VIII. Treatment of early/mild to moderate hypoparathyroidism

- Treatment for early/mild to moderate hypoparathyroidism typically includes oral calcium supplementation and possibly calcitriol and magnesium.
- A typical daily intake of elemental calcium, ranging from 400 to 1200 mg, can be effectively administered orally in divided doses. This is equivalent to consuming 1 to 3 grams of calcium carbonate, which is roughly equivalent to taking 2 to 6 TUMS tablets per day.
- Calcium carbonate, which contains 40% elemental calcium, and calcium citrate, with 21% elemental calcium, are the most used forms of calcium supplements. It is advisable to take these supplements with meals.
- Calcium carbonate necessitates an acidic environment for dissolution. Therefore, individuals taking proton pump inhibitors, older individuals with reduced stomach acid (achlorhydria), or those who have undergone gastric bypass surgery may find calcium citrate more suitable, as it does not rely on

an acidic environment for absorption. Some patients have reported experiencing fewer gastrointestinal side effects with calcium citrate, and it is available in smaller tablet sizes that are easier to swallow. Chewable and liquid options are also available for both forms.

- To ensure proper absorption, it is important to separate the intake of oral calcium from oral thyroid hormone replacement. Levothyroxine, a thyroid hormone replacement, should be taken one hour before or three hours after consuming calcium supplements. Additionally, if oral calcium is prescribed three times daily, rather than every eight hours, it may contribute to early morning hypocalcemia due to the extended fasting period during sleep.
- If a patient is experiencing symptomatic hypocalcemia, and their serum calcium levels are consistently declining or remain below 7 mg/dL, it is advisable to consider adding calcitriol to their treatment regimen. Typically, a dosage of 0.25–0.5 micrograms is administered twice daily.
- Additionally, it's worth noting that magnesium deficiency can hinder the release and activity of parathyroid hormone (PTH). Therefore, if a patient with normal kidney function has a serum magnesium level below 1.6 mg/dL, magnesium supplementation with 400 mg of magnesium oxide, taken once or twice daily, can help accelerate calcium recovery. This supplementation may also alleviate the constipation often associated with high-dose calcium replacement therapy.

IX. Treatment of progressive/symptomatic hypoparathyroidism

- If severe hypocalcemia develops despite oral calcium and calcitriol therapy, perform a 12-lead EKG, measure the corrected QT interval, and administer IV calcium.
    - Administering calcium through an intravenous (IV) bolus, which involves giving 1–2 grams of calcium gluconate (equivalent to 93 mg of elemental calcium in one vial of calcium gluconate) in a 50 mL solution of 5% dextrose over a 20-minute infusion, is the fastest method to rapidly raise serum calcium levels. However, it is also the least long-lasting approach.
    - Alternatively, using a calcium drip or slow IV infusion offers more consistent and sustained blood calcium levels. This method allows for adjustments to be made by monitoring calcium levels through serial measurements, ensuring that calcium remains within the lower end of the normal range.
    - For peripheral IV repletion, calcium gluconate is the preferred choice, providing 90 mg of elemental calcium per 10 mL of solution. Calcium

chloride, which contains 270 mg of elemental calcium per 10 mL, can cause issues such as phlebitis and local tissue necrosis when administered through peripheral lines. To mitigate these risks, it is essential to either use a central line for calcium chloride delivery or dilute it to approximately one-third of its concentration for peripheral administration.

    - It is important to note that initiating a calcium drip also requires electrocardiographic monitoring due to the potential risk of calcium overdose. Patients with severe hypocalcemia are prone to cardiac instability, QTc prolongation, or even the development of a condition called torsades de pointes. When a patient is receiving a calcium drip, it is advisable to increase their oral calcium and calcitriol doses as soon as feasible and gradually reduce the drip as tolerated.

- Thiazide diuretics can be considered if calcium control remains difficult.
    - If no contraindications exist, hydrochlorothiazide 12.5–50 mg daily may be effective, but it must be titrated to avoid hypotension.
- Approaches to the management of postoperative hypoPT are summarized in the table below:

Table 4. Approaches to Management of Postoperative Hypoparathyroidism

Approaches to Management of Postoperative HypoPT			
Setting	**Oral Calcium**[d]	**Calcitriol**	**Calcium I.V.**
Empiric prophylaxis[a]	0.5–1.25 g b.i.d.–t.i.d.	0.25– 0.5 µg b.i.d	N/A
Mild–moderate hypoPT[b]	1–3 g daily divided doses b.i.d.–t.i.d.	0.25– 0.5 µg b.i.d	N/A
Progressive/symptomatic hypoPT[c]	3–4 g daily in divided doses b.i.d. – t.i.d.	0.25– 1.0 µg b.i.d	IV bolus: 1–2 g Ca gluconate followed by continuous IV infusion
a Optimize 25 OH-vitamin D levels and serum magnesium. b Serum Calcium < 8.5 mg/dL, new-onset symptoms. c Serum Calcium < 7.0 mg/dL, persistent/severe symptoms despite therapy; check EKG for QTc prolongation. d Calcium carbonate, or equivalent in calcium citrate.			

X. Long-term management of hypoparathyroidism

- Long-term management aims to maintain serum calcium in the low normal range and includes calcium supplementation, and calcitriol.
- Long-term management aims to maintain calcium and phosphorus levels within normal ranges to prevent complications like calciphylaxis.
- Calcium supplementation doses may range up to 3500 mg daily, with most patients requiring 1500 mg. Therapy in two-three divided doses offers the best absorption.
- Calcitriol and vitamin D2 or D3 may be used for long-term management:
    - Most patients require 0.25 µg of calcitriol daily (0.25–4.0 µg/day). Vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol) are occasionally used for long-term management.
- Hydrochlorothiazide 12.5–50 mg daily may be added to reduce calcium supplementation needs and prevent hypercalciuria.
- Episodes of hypocalcemia or hypercalcemia may still occur in certain situations, requiring additional adjustments.
- Special considerations are needed for pregnancy, lactation, and patients with prior gastric bypass surgery (prior Roux-en-Y or other duodenal dissection).
- Long-standing hypoPT can have significant effects on quality of life and bone health.
- Recombinant human PTH (1–84) and teriparatide acetate are potential treatments for refractory hypoPT but require careful monitoring due to associated risks.

Table 5 provides key recommendations for the prevention and management of hypoPT:

Table 5. Key Recommendations for Prevention and Management of Hypoparathyroidism

Key Recommendations for Prevention and Management of HypoPT
• Conduct surgery to avoid removal or devascularization of parathyroid tissue. • Autotransplant devascularized or inadvertently removed normal parathyroid glands. • Either treat at-risk patients empirically with calcium, or measure calcium and/or PTH in the immediate postoperative period and treat according to evidence-based protocols.

- Titrate calcium with or without calcitriol to maintain eucalcemia and wean calcium and/or calcitriol when appropriate.
- Communication between providers is critical, since hypoPT may be prolonged and can negatively affect multiple organ systems.
- Inability to achieve independence from calcium by six months indicates permanent hypoPT.
- Recombinant human PTH analogues may be considered for patients with permanent hypoPT.
- Avoiding hypoPT is much less costly than treating hypoPT.

1.3 European Guidelines

1.3.1 European Society of Endocrinology Clinical Guideline: Treatment of Chronic Hypoparathyroidism in Adults (2015)

The purpose of this guideline published in 2015 by the European Society of Endocrinology (ESE) is to provide clinicians with guidance on the treatment and monitoring of chronic hypoPT. Evidence levels and grades of recommendations are outlined below[5]:

Table 6. ESE Quality of Evidence

GRADE Certainty Ratings of Recommendations	
Very low	The true effect is probably markedly different from the estimated effect.
Low	The true effect might be markedly different from the estimated effect.
Moderate	The authors believe that the true effect is probably close to the estimated effect.
High	The authors have a lot of confidence that the true effect is similar to the estimated effect.

Table 7. Strengths of Recommendations

Strength of recommendations	
Strong	Reasonably informed persons (clinicians, politicians, and patients) would want the management in accordance with the recommendation.
Weak	Most persons would still act in accordance with the guideline, but a substantial number would not

I. Diagnosis

A diagnosis of chronic hypoparathyroidism (HypoPT) should be considered when a patient exhibits hypocalcemia along with inappropriately low parathyroid hormone (PTH) levels.

Genetic testing and/or family screening for patients with HypoPT of unknown causes should be considered.

II. General Goals of Management in Chronic HypoPT

- Aim to maintain the patient's serum calcium level (albumin adjusted total calcium or ionized calcium) within the lower part or just slightly below the lower limit of the reference range, ensuring that patients are free from symptoms or signs of hypocalcemia (Very low quality of evidence).
- Ensure that 24-hour urinary calcium excretion falls within the sex-specific reference range (Very low quality of evidence).
- Keep serum phosphate levels within the reference range.
- Maintain the serum calcium–phosphate product below 4.4 $mmol^2/l^2$ (55 mg^2/dl^2) (Very low quality of evidence).
- Ensure serum magnesium levels remain within the reference range (Very low quality of evidence).
- Aim for an adequate vitamin D status (Very low quality of evidence).
- Personalize treatment to focus on the overall well-being and quality of life of the patient while striving to achieve therapeutic goals.
- Provide information and education to patients so they can recognize symptoms of hypo- or hypercalcemia and potential complications of their condition.

III. Treatment

- Treat all patients with chronic HypoPT who have symptoms of hypocalcemia and/or an albumin-adjusted serum calcium level < 2.0 mmol/l (< 8.0 mg/dl/ionized serum calcium levels < 1.00 mmol/l) (Very low quality of evidence).
- Consider offering treatment to asymptomatic patients with chronic HypoPT and an albumin-adjusted calcium level between 2.0 mmol/l (8.0 mg/dl) and the lower limit of the reference range to assess potential improvements in their well-being (Very low quality of evidence).
- Primary therapy involves using activated vitamin D analogues along with calcium supplements in divided doses (Very low quality of evidence).

- If activated vitamin D analogues are unavailable, treatment with calciferol (preferably cholecalciferol) is recommended.
- Adjust the doses of activated vitamin D analogues or cholecalciferol to keep patients symptom-free from hypocalcemia and maintain serum calcium levels within the target range (Very low quality of evidence).
- Provide vitamin D supplementation at a daily dose of 400–800 IU to patients treated with activated vitamin D analogues (Very low quality of evidence).
- Consider reducing calcium intake, implementing a sodium-restricted diet, and/or using a thiazide diuretic in patients with hypercalciuria (Very low quality of evidence).
- In cases of renal stones, evaluate risk factors and manage according to relevant international guidelines.
- For patients with hyperphosphatemia and/or an elevated calcium–phosphate product, consider dietary interventions and/or adjustments to calcium and vitamin D analogue treatment.
- If hypomagnesemia is present, consider measures to increase serum magnesium levels.
- Routine replacement therapy with PTH or PTH analogues is not recommended (Very low quality of evidence) (Very low quality of evidence).

IV. Monitoring

- Routinely monitor serum levels of ionized or albumin-adjusted total calcium, phosphate, magnesium, and creatinine (estimated glomerular filtration rate) along with assessing symptoms of hypocalcemia and hypercalcemia at regular intervals (e.g., every 3–6 months).
- Following therapy changes, perform weekly or bi-weekly biochemical monitoring.
- Consider monitoring 24-hour urinary calcium excretion at regular, but longer, intervals (e.g., once a year or every second year).
- Conduct renal imaging if patients exhibit symptoms of renal stone disease or if serum creatinine levels begin to rise.
- Monitor for signs or symptoms of co-morbidities at regular intervals (e.g., yearly).
- Routine monitoring of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) scans is not advised.

V. Special Circumstances

Autosomal dominant hypocalcemia

Patients with autosomal dominant hypocalcemia (ADH) receiving calcium and/or activated vitamin D analogues should undergo frequent monitoring due to the increased risk of hypercalciuria and renal complications.

Pregnancy and breastfeeding

- Treat pregnant women with activated vitamin D analogues and calcium supplements as in non-pregnant women.
- Regularly monitor serum ionized calcium during pregnancy and breastfeeding, aiming to maintain levels at the lower end of the normal range (albumin-adjusted total calcium is also acceptable).
- Inform the pediatrician and/or neonatologist about maternal HypoPT and involve them in the care and monitoring of the infant to address possible consequences of the maternal treatment and underlying disorder.

1.4 International Guidelines

1.4.1 First International Conference of the Management of Hypoparathyroidism (2016)

The First International Conference on the Management of Hypoparathyroidism held in 2015 represented a worldwide constituency with acknowledged interest and expertise in key basic, translational, and clinical aspects of hypoparathyroidism. Clinical guidelines and summary statements were published in 2016 and are summarized below. Evidence levels and grades of recommendation were not outlined[8].

I. Diagnosis and Evaluation

Diagnosis of hypoparathyroidism

- Diagnosis requires concurrent measurement of albumin-corrected or ionized serum calcium below the lower normal range and low or undetectable PTH levels.
- Diagnosis should be confirmed by second- or third-generation immunoassay on at least two occasions, with a minimum 2-week interval.
- Chronic hypoparathyroidism can be diagnosed in patients after anterior neck surgery, at least 6 months postoperatively.

- Total adjusted serum calcium accounts for serum albumin concentration influence: for every 1 g/dL reduction in serum albumin, total calcium is adjusted upward by 0.8 mg/dL.
- Ionized calcium is theoretically a more accurate physiological measurement but has technical limitations.
- Ionized calcium measurement requires proper blood collection conditions, calibration, and immediate processing.

The following table provides a summary on the diagnosis and evaluation of hypoparathyroidism:

Table 8. Diagnosis and Evaluation of Hypoparathyroidism

Diagnosis and Evaluation of Hypoparathyroidism
Hypocalcemia (albumin-adjusted) confirmed on at least two occasions separated by at least 2 weeks.
PTH concentration, by second- or third-generation immunoassay, that is undetectable or inappropriately low (ie, < 20 pg/mL) in the presence of hypocalcemia on at least two occasions.
Phosphate levels in the upper normal or frankly elevated range (helpful but not mandatory).
After neck surgery, chronic hypoparathyroidism is established only after 6 months.

Diagnostic evaluation

1. **Historical aspects**
    - Family history
    - Personal history of anterior neck surgery
    - Review for gastrointestinal, renal, and skeletal symptoms
    - Assessment of general quality of life
    - Review of medications and supplements
2. **Physical examination (key elements)**
    - Eye examination for cataracts and calcifications
    - Anterior neck examination for signs of previous surgery
    - Assessment of neuromuscular irritability (Chvostek's and Trousseau's signs)
    - Inspection of nail beds for fungal infection
    - Examination for mucosal candidiasis

- Evaluation of joint range of motion
- Assessment of skin for vitiligo

3. **Biochemical evaluation (key elements, assuming PTH confirmation)**
    - Chemistry panel including phosphate and magnesium
    - Measurement of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D
    - 24-hour urinary calcium excretion
    - Estimated or calculated glomerular filtration rate (GFR)
    - Biochemical stone risk profile, if indicated by the clinical situation
4. **Imaging studies**
    - Dual-energy x-ray absorptiometry
    - Skull x-ray to check for basal ganglia and other intracerebral calcifications
    - Abdominal imaging to identify renal stones and calcifications
5. **Genetic studies**
    - Consider genetic counseling and germline mutation testing if the patient's presentation suggests a genetic basis (e.g., young age, family history, multiple autoimmune features).

The following table provides a summary on the evaluation of hypoparathyroidism:

Table 9. Evaluation of Hypoparathyroidism

Evaluation of Hypoparathyroidism
Family history: History of hypoparathyroidism or other endocrine deficiency disease.
Personal history: Previous anterior neck surgery, other endocrine disease.
Physical examination • Ectopic calcifications (eg, eyes) • Signs of previous neck surgery • Chvostek's or Trousseau's sign • Nail beds for fungal infection • Mucosal candidiasis • Range of joint motion • Skin for vitiligo
Biochemical evaluation (after the diagnosis has been made)

- Phosphate
- Magnesium
- 25-hydroxyvitamin D
- 1,25-dihydroxyvitamin D
- BUN/creatinine
- 24-hour urine for creatinine clearance or eGFR, calcium excretion, and biochemical stone risk profile

Target organ imaging

- X-ray (skull)
- Renal ultrasound or computed tomography scanning
- BMD by dual-energy x-ray absorptiometry

Genetic studies: If a genetic basis is suspected (young age, family history, multiple endocrine gland failure)

II. Management of hypoparathyroidism

Acute hypocalcemia

- Hypoparathyroidism can sometimes lead to acute hypocalcemia due to factors like neck surgery, changing calcium and vitamin D needs, or noncompliance.
- Symptoms range from mild tingling to severe symptoms like muscle spasms, laryngospasm, or seizures.
- Urgent management of symptomatic hypocalcemia includes intravenous calcium gluconate in two steps: one or two ampules of a 10% solution of calcium gluconate, containing 90 –180 mg elemental calcium in 50 mL of 5% dextrose, over 10 to 20 minutes followed by a slower infusion of calcium gluconate, 0.5 to 1.5 mg/kg/h over an 8- to 10-hour period. The use of PTH in this context is limited.

Chronic hypocalcemia of hypoparathyroidism

- Traditional therapy involves careful use of calcium and active vitamin D (calcitriol or analogs), as well as parent vitamin D (cholecalciferol or ergocalciferol).
- Many practitioners will try to limit the amount of calcium supplementation by being more proactive with the use of active vitamin D.
- Thiazide diuretics can help in cases of hypercalciuria.

- Six goals of chronic management: prevent hypocalcemia symptoms, maintain serum calcium slightly below normal (ie, no more than 0.5 mg/dL below normal), maintain calcium-phosphate product below 55 mg2/dL2 (4.4 mmol2/L2), avoid hypercalciuria and hypercalcemia, and prevent renal and other extraskeletal calcifications.
- Frequent serum calcium monitoring (weekly or monthly) is recommended during dose adjustments, then less frequent once stable (twice a year on average).
- In patients who have had a tendency to become hypercalciuric, 24-hour urine calcium measurements are recommended.
- Phosphate binders or low-phosphate diets are recommended only for severe hyperphosphatemia (above 6.5 mg/dL).

The following table provides a summary on the conventional management of chronic hypoparathyroidism:

Table 10. Conventional Management of Chronic Hypoparathyroidism

Conventional Management of Chronic Hypoparathyroidism
• Dietary calcium and oral calcium supplements • Active vitamin D or analogs • Magnesium • Thiazide diuretics when necessary to help manage hypercalciuria and low salt diet. • Phosphate binders and low phosphate diet, if necessary to control hyperphosphatemia

1. Calcium supplementation

Calcium carbonate is the mainstay of calcium supplementation, as it can be administered more efficiently, 40% of it being elemental calcium.

Calcium citrate (20% elemental calcium), the other most common form of calcium supplementation, can also be helpful in certain circumstances, such as when achlorhydria is present, in the setting of proton pump inhibitor therapy, or in patients who complain of constipation with calcium carbonate. The amount of calcium supplementation required varies enormously, with amounts as high as 9 grams per day reportedly used.

2. Active and parental vitamin D

Active vitamin D (1,25-dihydroxyvitamin D; calcitriol) compensates for impaired renal conversion in hypoparathyroidism. Dosage varies but is typically between 0.25 and 2 µg daily. Other vitamin D formulations that undergo activation in the liver are used outside the United States, such as 1α-hydroxyvitamin D (alfacalcidol) and dihydrotachysterol.

Titrating upward the use of active vitamin D formulations can help to reduce the amount of calcium supplementation patients require.

Parental vitamin D forms (vitamin D2 [ergocalciferol] or vitamin D3 [cholecalciferol]) are also used. Parental vitamin D may have non-skeletal benefits.

3. Thiazide diuretics

Used to promote renal tubular calcium retention in cases of hypercalciuria, they are contraindicated in certain cases (e.g., autoimmune polyendocrine syndrome type 1 with adrenal insufficiency).

Serum potassium and magnesium should be monitored to prevent hypokalemia or hypomagnesemia.

Monitoring of conventional management with calcium and vitamin D

- Monitoring frequency depends on treatment stability.
- Frequent monitoring during dosage adjustments.
- Annual renal function assessment by a 24-hour urine collection for calcium and creatinine excretion along with a measured creatinine clearance or estimated GFR (eGFR).
- Skeletal monitoring as recommended by clinical guidelines.

The following table provides a summary on the monitoring of conventional therapy:

Table 11. Monitoring Guidelines on Conventional Therapy

Monitoring Guidelines on Conventional Therapy

• Calcium, phosphate, magnesium, BUN/creatinine and eGFR: yearly or more frequently if the clinical situation is appropriate.
• 24-hour urine for calcium and creatinine
• As clinically indicated:
  ○ Renal imaging (for nephrolithiasis/nephrocalcinosis)
  ○ Ophthalmological exam (cataracts)

- Central nervous system imaging (basal ganglia and other sites of calcification)
- BMD

Advances in chronic management: PTH peptides

- Recombinant human PTH (1-84) was FDA-approved for hypoparathyroidism management in 2015.
- PTH (1-34) and PTH (1-84) have shown promise in controlling symptoms and reducing calcium and active vitamin D needs.
- Monitoring required during the transition to PTH therapy. Potential benefits include reduced complications of conventional therapy.
- The FDA approved rhPTH (1-84) with a "black box" warning because of the history of rat osteosarcoma using all forms of PTH that have been studied so far but did not limit the duration of use.

Selection of patients for rhPTH (1-84) therapy

- Consider PTH (1-84) for patients with poorly controlled chronic hypoparathyroidism of any cause except ADH (autosomal dominant hypocalcemia) or high calcium and vitamin D requirements.
- Criteria for considering PTH therapy include unstable serum calcium, renal complications, hypercalciuria, high calcium-phosphate product, excessive oral medications, or gastrointestinal absorption issues.
- PTH therapy is costly.
- The table below shows the indications for Considering the Use of rhPTH (1-84) in Hypoparathyroidism:

Table 12. Indications for Considering the Use of rhPTH (1-84) in Hypoparathyroidism

Indications for Considering the Use of rhPTH (1-84) in Hypoparathyroidism
1. Inadequate control of the serum calcium concentration (this could be due to intercurrent illness, compliance, absorption, or intrinsic changes in requirements that are beyond facile correction with calcium and active vitamin D) 2. Oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g of calcium or >1.5 µg of active vitamin D or >3.0 µg of the 1-α vitamin D analog**.** 3. Hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (<60 mL/min)

4. Hyperphosphatemia and/or calcium-phosphate product that exceeds 55 mg^2/dL^2 (4.4 $mmol^2/L^2$)
5. A gastrointestinal tract disorder that is associated with malabsorption**.**
6. Reduced quality of life

Management approach with PTH (1-84)

- Initiate with the lowest dose (50 µg) subcutaneously into the thigh. The dose of rhPTH (1-84) can be increased in 25-µg steps to 100 µg daily. There are no factors that can predict what ultimate dose will work best for a given patient.
- Simultaneously reduce active vitamin D by 50%. An alternative approach would be to start by reducing oral calcium by 50% instead of active vitamin D.
- Monitor serum calcium within the first week and adjust dose as needed.
- Goals include minimizing active vitamin D, reducing calcium supplementation, and maintaining lower normal serum calcium.
- If there is a need to discontinue the use of rhPTH (1-84) for any reason, it is crucial to pay close attention to the immediate signs of hypocalcemia and to ensure that the 25-hydroxyvitamin D levels in all patients remain within the generally acceptable range of 20 to 50 ng/mL. Moreover, when adjusting or initiating calcium and active vitamin D therapy, it should be done cautiously, with frequent monitoring for any indications or symptoms of hypocalcemia.

Safety considerations

- No evidence of osteosarcoma risk in human subjects using PTH.
- The “black box” warning for rhPTH (1-84) thus reiterates this cautionary note, although rhPTH (1-84) has no therapeutic time limit for treatment.
- Hypercalcemia can occur but is not a common issue with PTH (1-84) therapy.

1.4.2 Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop (2022)

The 2022 International Task Force guidelines for chronic hypoparathyroidism update the original guidelines published in 2016 and include new information from literature published since then. Chronic postsurgical hypoparathyroidism is now defined as lasting for at least 12 months after surgery, rather than 6 months. Chronic postsurgical hypoparathyroidism may be predicted by serum PTH. The main recommendations are detailed below. Evidence levels and grades of recommendations are outlined in tables 13 and 14[9]:

Table 13. GRADE Certainty Ratings of Recommendations

GRADE Certainty Ratings of Recommendations	
Very low	The true effect is probably markedly different from the estimated effect.
Low	The true effect might be markedly different from the estimated effect.
Moderate	The authors believe that the true effect is probably close to the estimated effect.
High	The authors have a lot of confidence that the true effect is similar to the estimated effect.

Table 14. Strengths of Recommendations

Strength of Recommendations	
Strong	A strong recommendation was made when the desirable effects were much greater than undesirable effects or vice versa and is worded as "we recommend.
Weak	A weak recommendation was made if there was low certainty of evidence or a close balance between desirable and undesirable effects and is worded as "we suggest."

1. **How to diagnose chronic hypoPT (un-GRADEd recommendation)**
    - Observe hypocalcemia (low ionized serum calcium or total serum calcium adjusted for albumin) in conjunction with an undetectable, low, or inappropriately normal intact PTH (using either a second- or third-generation assay) on two separate occasions at least 2 weeks apart.
    - Additional indicators that support the diagnosis due to low PTH levels include elevated serum phosphorus, decreased levels of 1,25-dihydroxyvitamin D (1,25(OH)2D), and an increase in the urinary fractional excretion of calcium.
    - In cases of postsurgical hypoPT, if the condition persists for more than 12 months after surgery, it is considered permanent.

2. **Minimizing the risks of chronic postsurgical hypoPT (un-GRADEd recommendation)**
    - The panel recommends avoiding accidental removal of parathyroid glands during surgery and suggests using intraoperative parathyroid autotransplantation only when parathyroidectomy has occurred unintentionally.

3. **What is the value of determining serum calcium and PTH post-thyroidectomy to predict future permanent postsurgical hypoPT? (GRADEd recommendation)**
    - The panel recommends measuring PTH levels within 12–24 hours after total thyroidectomy to predict the likelihood of not developing permanent postsurgical hypoPT (strong recommendation, moderate quality evidence).
    - If PTH values are >10 pg/mL (1.05 pmol/L) during this time frame, the risk of permanent hypoPT is low, and there is no long-term need for treatment with active vitamin D and calcium supplements above the recommended daily allowance. However, patients with PTH values <10 pg/mL (1.05 pmol/L) 12–24 hours post-surgery may still recover from temporary hypoPT.

4. **What is the role of genetic testing in the diagnosis and evaluation of chronic hypoPT? (un-GRADEd recommendations)**
    - Genetic testing is recommended for patients with nonsurgical hypoPT who have a positive family history of nonsurgical hypoPT, exhibit syndromic features, or are under 40 years of age.
    - Genetic testing for autoimmune regulator (AIRE) gene variants is suggested for patients with nonsurgical hypoPT who display clinical features of autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome (APECED).
    - The panel advises against labeling patients as having "autoimmune hypoPT" if they do not have APECED because there are no definitive diagnostic tests for polygenic autoimmune hypoPT.

5. **What are the most common symptoms and complications of chronic hypoPT reported in the literature? (GRADEd recommendation)**
    - Observational studies have identified various complications associated with chronic hypoPT when compared to individuals with normal parathyroid function. These complications include cataracts (17%), infections (11%), nephrocalcinosis/nephrolithiasis (15%), renal insufficiency (12%), seizures (11%), depression (12%), ischemic heart disease (7%), and arrhythmias (7%). (Percentages represent median values among all studies.)

6. **What is the optimal monitoring strategy for chronic hypoPT?**
    - Systematic Current Practice Survey (low-quality recommendations)

Table 15. Optimal Monitoring Strategy for Chronic Hypoparathyroidism

	New patients	Follow-up for stable patients**
Serum creatinine, estimated glomerular filtration rate (eGFR), calcium (either ionized or albumin-adjusted), magnesium, phosphorus	√	Every 3– 12 months
25-hydroxyvitamin D	√	Every 6– 12 months
24-hour urine for creatinine and calcium	√	Every 6– 24 months
**For unstable patients: Frequently measure serum calcium and phosphorus as clinically indicated		

- The Panel also suggests the following (non-survey based):
    - Complete a baseline assessment for the presence of renal calcification or stones with renal imaging.
    - Monitor serum calcium (ionized or albumin-adjusted) within several days of a significant change in medical treatment.

7. How to manage patients with hypoPT

- GRADEd recommendations:
    - For patients with chronic hypoPT, the primary recommendation is to initiate conventional therapy as the first-line treatment (weak recommendation, low-quality evidence). In cases where conventional therapy proves unsatisfactory, the panel considers the use of parathyroid hormone.
- Un-GRADEd recommendations:
    - Start treatment with both calcium and an active vitamin D analogue, aiming to elevate serum calcium to the target range, specifically the lower half of the normal reference range or just slightly below it. The optimal balance between calcium and the active vitamin D analogue doses is currently unclear.
    - The goal is to alleviate symptomatic hypocalcemia while preventing hypercalciuria.
    - While titrating calcium and active vitamin D analogue therapy, it's important to avoid hypercalciuria and aim for low-normal plasma

calcium levels. The suggested target is a 24-hour urinary calcium level of <6.25 mmol/24 hours or 250 mg/24 hours for adult women and <7.5 mmol/24 hours or 300 mg/24 hours for adult men. Although there is no specific data on renal stones in hypoPT patients, panel members infer that hypercalciuria might pose a higher risk of renal stones and therefore aim to prevent it.

- Avoid hyperphosphatemia by administering calcium supplements with meals to act as phosphate binders, implementing a low-phosphate diet in adults if necessary, and using active vitamin D analogue therapy judiciously. Currently, there is no evidence of hyperphosphatemia causing ectopic calcification in hypoPT.
- Ensure that plasma magnesium levels are normalized and provide magnesium supplements as tolerated by the patient.
- Target a 25-hydroxyvitamin D (25(OH)D) level within the normal reference range (75–125 nmol/L).
- Consider using thiazide diuretics to treat hypercalciuria in combination with a low-sodium diet, closely monitoring blood pressure, serum magnesium, potassium, and renal function.
- PTH replacement therapy should be considered for patients who are not adequately controlled with conventional therapy. Inadequate control includes symptomatic hypocalcemia, hyperphosphatemia, renal insufficiency, hypercalciuria, or poor quality of life.
- Patients with poor compliance, malabsorption issues, or intolerance to high doses of calcium and active vitamin D may benefit from PTH therapy. Patients requiring high doses of conventional therapy (i.e., calcium > 2 g/day or active vitamin D > 2 mcg/day) may also find PTH therapy beneficial.

8. Recommendations for managing hypoPT during pregnancy and lactation (un-GRADEd recommendations)

- Aim to maintain serum calcium (ionized or albumin-adjusted) in the mid to low normal reference range throughout pregnancy.
- Target serum phosphorus, magnesium, and 25-hydroxyvitamin D (25OHD) levels within the normal reference range.
- Regularly monitor serum calcium (ionized or albumin-adjusted) every 3–4 weeks during pregnancy and lactation, with increased frequency in the months surrounding childbirth and in response to symptoms of hypercalcemia or hypocalcemia.

- Collaborate closely with obstetricians to optimize pregnancy outcomes and coordinate with pediatric teams to ensure appropriate postnatal monitoring for transient neonatal hypo- or hypercalcemia.
- Avoid the use of thiazide diuretics and PTH or PTH analogues during pregnancy.

1.5 Systematic Reviews & Meta Analyses

The table below tackles a systematic review and meta-analyses issued in **2022** for Hypoparathyroidism.

Table 16. Systematic Review and Meta-Analysis for Hypoparathyroidism

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Yao et al. (2022)	Parathyroid Hormone Therapy for Managing Chronic Hypopara-thyroidism: A Systematic Review and Meta-Analysis[10]	To investigate the benefits and harms of PTH therapy and conventional therapy in the management of patients with chronic hypopara-thyroidism.	• **Patient-important outcomes**: major complications related to chronic hypoparathyroidism, including nephrolithiasis, renal failure, seizures, arrhythmia, ischemic heart disease, depression, cataracts, infection, and all-cause mortality. • **Surrogate outcomes**: hypocalcemia, hypercalcemia, hypercalciuria, 24-hour urine calcium excretion, serum calcium, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-dihydroxy vitamin	• None of the studies reported outcomes related to nephrocalcinosis/ nephrolithiasis, seizures, arrhythmia, ischemic heart disease, cataracts, fracture, infection, or all-cause mortality. • Studies suggest that PTH therapy probably achieves a small benefit (mean difference [MD] 3.4, 95% confidence interval [CI] 1.5–5.3, minimally important difference 3.0, moderate certainty). • Two studies reported that PTH (1–84) therapy resulted in more patients reaching a 50% or greater reduction in the doses of active vitamin D and calcium compared to conventional therapy (RR = 6.5, 95% CI 2.5–16.4, 385 more per 1000 patients, high certainty evidence). • In terms of adverse events, five studies were included, and

				D3, serum magnesium, serum alkaline phosphatase, serum osteocalcin, urine deoxypyridinoline, urine pyridinoline, mean creatinine clearance levels, and bone mineral density (BMD).	both the PTH and conventional therapy groups experienced serious adverse events at a rate of 9%. However, there was no substantial evidence of significant differences between the two groups based on the limited data available, as indicated by a risk ratio (RR) of 1.14 (95% CI 0.6–2.2) with an additional 9 events per 1000 patients. Study discontinuation due to adverse events showed no significant disparity between the groups, with an RR of 1.0 (95% CI 0.1–9.8) and no additional events per 1000 patients. Notably, thirst was significantly more prevalent in the PTH (1–84) group than in the conventional therapy group (RR = 6.5, 95% CI 1.2–34.2), resulting in 77 more events per 1000 patients. • Regarding surrogate outcomes, PTH therapy was associated with higher serum calcium levels (MD 0.11 mmol/L, 95% CI 0.02–0.20) but lower serum phosphorus levels (MD -0.2 mmol/L, 95% CI -0.4 to -0.03). It also led to lower serum 25-hydroxyvitamin D levels (MD -9.2 ng/mL, 95% CI -12.2 to -6.1) and decreased serum magnesium levels (MD -0.06 mmol/L, 95% CI -0.1 to -0.01). Additionally, patients receiving PTH (1–84) had a higher incidence of hypercalcemia (RR = 2.4, 95% CI 1.2–5.04). There was

					no compelling evidence demonstrating a significant impact of PTH (1–34) versus conventional therapy on creatinine clearance, with an MD of 3.9 mL/min (95% CI -2.4 to 10.3). Both groups exhibited similar mean renal function.

Section 2.0 Drug Therapy

2.1 Calcium Replacement

Table 17. Calcium Drug Information

SCIENTIFIC NAME **Calcium Replacement**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E20.9
Drug Class	Calcium Salt; Electrolyte Supplement
Drug Sub-class	
ATC Code	A12AA07 A12AA04 A12AA03 A12AA20
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for injection Solution Film-coated tablet Tablet Syrup Solution for infusion Intravenous infusion
Route of Administration	Intravenous use Oral use
Dose (Adult) [DDD]*	**Oral:** Initial: 1 to 4 g/day of elemental calcium administered in 2 to 3 divided doses; adjust dose as needed to control symptoms and maintain albumin-corrected calcium levels in the low-normal range

	Initial bolus dose(s): IV: Add 1 or 2 g (10 or 20 mL of a 10% solution) to 50 mL of D5W or NS (equivalent to ~90 or ~180 mg elemental calcium). Infuse over 10 to 20 minutes; may repeat bolus dose after 10 to 60 minutes if symptoms persist. If hypocalcemia is expected to persist (eg, hypoparathyroidism, pancreatitis), follow bolus dose(s) with a continuous IV calcium infusion. **Continuous infusion: IV:** Add 11 g (110 mL of a 10% solution) to 890 mL of D5W or NS (equivalent to ~1 g elemental calcium in a final total volume of 1,000 mL). Initiate infusion at 50 to 100 mL/hour (equivalent to ~50 to 100 mg/hour of elemental calcium; adjust dose to maintain albumin-corrected serum calcium levels at the low end of normal. Initiate oral calcium and vitamin D supplements as soon as possible; once an effective oral regimen is achieved, taper IV calcium infusion slowly (eg, over 24 to 48 hours)
Maximum Daily Dose Adults*	2g elemental calcium (IV), 4g elemental calcium (PO)
Dose (pediatrics)	Hypocalcemia, asymptomatic: Limited data available: elemental calcium: **Oral**: 30 to 75 mg/kg/day in 4 to 5 divided doses Mild to moderate symptoms: **IV Intermittent**: <17 years: calcium gluconate: IV: 29 to 60 mg/kg/dose every 6 hours. ≥17 years: calcium gluconate: IV: 1,000 to 2,000 mg/dose every 6 hours. **Continuous IV Infusion**: <17 years: Initial: calcium gluconate: IV: 8 to 13 mg/kg/hour. ≥17 years: Initial: calcium gluconate: IV: 5.4 to 21.5 mg/kg/hour.

	Severe symptoms (eg, seizures, tetany): calcium gluconate: **IV, Intraosseous**: 100 to 200 mg/kg/dose over 5 to 10 minutes, maximum dose: 1,000 to 2,000 mg/dose; may repeat as needed or follow with a continuous IV infusion of 8 to 32 mg/kg/hour
Maximum Daily Dose Pediatrics*	2,000 mg/dose
Adjustment	Do not use IV calcium as initial therapy in patients with chronic kidney disease who are asymptomatic or who have stable hypocalcemia with only mild symptoms (eg, paresthesias): Initiate with lowest dose of the recommended dosage range. eGFR <60 mL/minute/1.73 m2: There are no specific dosage adjustments recommended; however, a positive calcium balance has been associated with increased mortality in patients with chronic kidney disease (CKD). Daily elemental calcium intake (including dietary sources and calcium-based phosphate binders) recommendations in patients with CKD G3A through G5D (patients on hemodialysis, peritoneal dialysis) vary; one guideline recommends not exceeding 2,000 mg/day, but more recent short-term studies in nondialysis patients suggest limiting intake to 800 to 1,000 mg/day. Decisions regarding calcium carbonate use and dose must be individualized to the patient, and hypercalcemia should be avoided. No dosage adjustments in hepatic impairment.: subsequent doses should be guided by serum calcium concentrations. In patients in the anhepatic stage of liver transplantation, equal rapid increases in ionized

	concentrations occur suggesting that calcium gluconate does not require hepatic metabolism for release of ionized calcium
Prescribing edits*	CU
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Correct concurrent hypomagnesemia if present and initiate vitamin D replacement as soon as feasible	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Frequency not defined: Calcium Gluconate:** • Cardiovascular: Arrhythmia, bradycardia, cardiac arrest, decreased blood pressure, syncope, vasodilation • Central nervous system: Anxiety, feeling hot • Gastrointestinal: Unusual taste (chalky) • Neuromuscular & skeletal: Tingling sensation **Calcium Carboonate: 1-10%** • Central nervous system: Headache, laxative effect • Endocrine & metabolic: Hypercalcemia, hypophosphatemia, milk-alkali syndrome (with very high, chronic dosing and/or renal failure [headache, nausea, irritability, and weakness or

	alkalosis, hypercalcemia, renal impairment]) • Gastrointestinal: Abdominal pain, anorexia, constipation, flatulence, hyperacidity (acid rebound), nausea, vomiting, xerostomia
Drug Interactions*	(From the monograph of calcium carbonate) X Baloxavir Marboxil Depends on Route X Calcium Acetate X Cefditoren X Levonadifloxacin Depends on Route X Unithiol Depends on Route D Acalabrutinib Depends on Dosage Form D Alendronate Depends on Route D Alpha-Lipoic Acid Depends on Route D Atazanavir D Belumosudil D Bictegravir Depends on Route D Bisacodyl D Bismuth Subcitrate D Bosutinib D Budesonide (Systemic) D Cabotegravir Depends on Route D Cefuroxime Depends on Route D Chloroquine D Ciprofloxacin (Systemic) Depends on Route D Clodronate Depends on Route D Cortisone D Dabigatran Etexilate Depends on International labeling DDasatinib D Deferiprone Depends on Route D Deflazacort D Delafloxacin Depends on Route D Delavirdine D Demeclocycline Depends on Route

	D DexAMETHasone (Systemic) D Dolutegravir Depends on Route D Doxycycline Depends on Route D Eltrombopag Depends on Route D Elvitegravir D Enoxacin Depends on Route D Erdafitinib D Erlotinib D Estramustine Depends on Route D Etidronate Depends on Route D Ferric Citrate Depends on Route D Ferric Maltol Depends on Route D Ferrimanitol Ovoalbumin Depends on Route D Ferrous Fumarate Depends on Route D Ferrous Gluconate Depends on Route D Ferrous Sulfate Depends on Route D Fludrocortisone D Fosinopril D Gefitinib D Gemifloxacin Depends on Route D Hydrocortisone (Systemic) D Hyoscyamine Depends on Dosage Form and Route D Ibandronate Depends on Route D Infigratinib DIron Acetyltransferrin Depends on Route D Itraconazole Depends on Brand Name D Ketoconazole (Systemic) D Lanthanum D Ledipasvir D LevoFLOXacin (Systemic) Depends on Route D Levoketoconazole D Levothyroxine Depends on Route D Liothyronine Depends on Route D Lomefloxacin Depends on Route

	D Lymecycline Depends on Route D Mesalamine Depends on Brand Name D Methenamine D MethylPREDNISolone D Minocycline (Systemic) Depends on Route D Multivitamins/Fluoride (with ADE) D Multivitamins/Minerals (with ADEK, Folate, Iron) D Nalidixic Acid Depends on Route D Neratinib D Nilotinib D Norfloxacin Depends on Route D Ofloxacin (Systemic) Depends on Route D Omadacycline Depends on Route D Oxytetracycline Depends on Route D PAZOPanib D Pefloxacin Depends on Route D PenicillAMINE Depends on Route D Pexidartinib D Pipemidic Acid Depends on Route D Polysaccharide-Iron Complex Depends on Route D Potassium Phosphate Depends on Route D PrednisoLONE (Systemic) D PredniSONE D Prulifloxacin Depends on Route D Raltegravir D Rilpivirine Depends on Route D Riociguat D Risedronate Depends on Route D Roxadustat Depends on Route D Sarecycline Depends on Route D Selpercatinib D Sodium Feredetate Depends on Route

	D Sodium Phosphates Depends on Route D Sotalol D Sotorasib D Sparfloxacin Depends on Route D Sparsentan D Strontium Ranelate Depends on Route D Sucralfate D Sulpiride D Tetracycline (Systemic) Depends on Route D Thyroid, Desiccated Depends on Route D Tiludronate Depends on Route D Trientine Depends on Route D Velpatasvir D Zabofloxacin Depends on Route
Special Population	Constipation and gas may be significant in elderly with calcium gluconate/carbonate but is usually mild. When using it in the elderly, check albumin status and make appropriate decisions concerning reference serum concentrations. Elderly, especially the ill, often have low albumin due to malnutrition.
Pregnancy	Calcium crosses the placenta. The amount of calcium reaching the fetus is determined by maternal physiological changes. Calcium requirements are the same in pregnant patients and nonpregnant females. Calcium is required for fetal growth. Intestinal absorption and urinary excretion of calcium increase during pregnancy. The amount of calcium reaching the fetus is determined by maternal physiological changes which are generally not influenced by

	maternal diet or supplementation. High doses of calcium carbonate should be avoided.
Lactation	Calcium is present in breast milk. Calcium is required for milk production. The amount of calcium in breast milk is homeostatically regulated and not altered by maternal calcium intake. Calcium requirements are the same in lactating patients and nonlactating females. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. Chronic use of high doses of calcium carbonate as an antacid may cause severe hypercalcemia presenting as milk-alkali syndrome in the mother.
Contraindications	Hypercalcemia; concomitant use of IV calcium gluconate with ceftriaxone in neonates (≤28 days of age). Patients with ventricular fibrillation; patients with asystole and electromechanical dissociation; concomitant use of IV calcium chloride with ceftriaxone in neonates (≤28 days of age). Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Hypersensitivity to any component of the formulation
Monitoring Requirements	**IV:** Serum calcium every 4 to 6 hours (during intermittent infusion), every 1 to 4 hours (during continuous infusion), or every 4 hours in patients with renal impairment; albumin, phosphate, and magnesium; vitals and ECG when appropriate. Monitor infusion site.

	Calcium supplementation in hypoparathyroidism: Note: Frequency of measurement is dependent upon on how stable a patient is to a given dosage regimen with more frequent measurements (eg, weekly) required initially during dosage titration. Once patient is well controlled, monitoring may be required on a yearly or twice-yearly basis. Serum calcium, phosphate, and magnesium; renal function (ie, 24-hour urinary calcium and creatinine, blood urea nitrogen [BUN]), measured CrCl or estimated glomerular filtration rate (eGFR); renal imaging (every 5 years in asymptomatic patients with a history of renal lithiasis or calcinosis or more frequently as indicated); CNS imaging (basal ganglia and other sites of calcification), ophthalmologic exam, and/or BMD as clinically indicated
Precautions	***Concerns related to adverse effects:*** • Extravasation: Parenteral calcium is a vesicant; ensures proper catheter or needle position prior to and during infusion. Avoid extravasation; adverse events from extravasation can be devastating (eg, profound tissue necrosis). Monitor the IV site closely. • GI effects: Constipation, bloating, and gas are common with oral calcium supplements (especially carbonate salt). • Hypercalcemia: Chronic hypercalcemia may result in generalized vascular and soft tissue calcification, exacerbate nephrolithiasis, and has been associated with increased mortality in adults with chronic kidney disease

	Disease-related concerns: • Achlorhydria: Calcium carbonate absorption is impaired in achlorhydria; administration is followed by increased gastric acid secretion within 2 hours of administration especially with high doses. Common in older adults, use an alternate salt (eg, citrate) and administer with food. • Hyperphosphatemia: Use with caution in patients with severe hyperphosphatemia as elevated levels of phosphorus and calcium may result in soft tissue and pulmonary arterial calcium-phosphate precipitation. • Hypokalemia: Use with caution in patients with severe hypokalemia as acute rises in serum calcium levels may result in life-threatening cardiac arrhythmias. • Hypomagnesemia: Hypomagnesemia is a common cause of hypocalcemia; therefore, correction of hypocalcemia may be difficult in patients with concomitant hypomagnesemia. Evaluate serum magnesium and correct hypomagnesemia (if necessary), particularly if initial treatment of hypocalcemia is refractory. • Kidney stones (calcium-containing): Use caution when administering calcium supplements to patients with a history of kidney stones. • Renal impairment: Use with caution in patients with chronic renal failure to avoid hypercalcemia; frequent monitoring of serum calcium and phosphorus is necessary.

	Concurrent drug therapy issues: • Ceftriaxone: Ceftriaxone may complex with calcium causing precipitation. Fatal lung and kidney damage associated with calcium-ceftriaxone precipitates has been observed in premature and term neonates. Due to reports of precipitation reaction in neonates, do not coadminister ceftriaxone with calcium-containing solutions, even via separate infusion lines/sites or at different times in any neonate. Ceftriaxone should not be administered simultaneously with any calcium-containing solution via a Y-site in any patient. However, ceftriaxone and calcium-containing solutions may be administered sequentially of one another for use in patients other than neonates if infusion lines are thoroughly flushed (with a compatible fluid) between infusions. • Digoxin: Use with caution in digitalized patients; hypercalcemia may precipitate cardiac arrhythmias. ***Dosage form specific issues:*** • Aluminum: The parenteral product may contain aluminum; toxic aluminum concentrations may be seen with high doses, prolonged use, or renal dysfunction. Premature neonates are at higher risk due to immature renal function and aluminum intake from other parenteral sources. Parenteral aluminum exposure of >4 to 5 mcg/kg/day is associated with CNS and bone toxicity; tissue loading may occur at lower doses (Federal Register 2002). See manufacturer's labeling.

	• Appropriate product selection: Multiple salt forms of calcium exist; close attention must be paid to the salt form when ordering and administering calcium; incorrect selection or substitution of one salt for another without proper dosage adjustment may result in serious over or under dosing. • IV administration: Avoid too-rapid IV administration (do not exceed 200 mg/minute in adults and 100 mg/minute in pediatric patients), unless patient is in cardiac arrest; may result in vasodilation, hypotension, bradycardia, arrhythmias, syncope, and cardiac arrest. • Oral administration: Administering oral calcium with food and vitamin D will optimize calcium absorption. • Topical administration: Avoid contact with eyes; not for oral administration. • Tartrazine: Some products may contain tartrazine, which may cause allergic reactions in susceptible individuals.
Black Box Warning	N/A
REMS*	N/A

The following table shows the percentage of elemental calcium found in each calcium salt:

Table 18. Percentage of Elemental Calcium Found in Each Calcium Salt

Type of Calcium	% of Elemental Calcium
Carbonate	40.0
Citrate	30.0
Phosphate (dibasic)	24.4
Phosphate (tribasic)	38.8
Gluconate	9.0

Lactate	18.4
Lacto Gluconate	12.9

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hypoparathyroidism treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Calcium.**

Table 19. Calcium HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Calcium	NICE	No recommendations for this indication.
	CADTH	No recommendations for this indication.
	HAS	No recommendations for this indication.
	IQWIG	No recommendations for this indication.
	PBAC	No recommendations for this indication

CONCLUSION STATEMENT – Calcium

Calcium supplementation is part of the standard therapy for the management of hypoparathyroidism. While there are no recommendations by major HTA bodies for the use of calcium in hypoPT, the various calcium salts have been available on the market for years and mostly marketed as over the counter (OTC) drugs, leading to a relatively low cost of treatment.

2.2 Vitamin D Supplement

Table 20. Vitamin D Drug Information

SCIENTIFIC NAME **Vitamin D: CHOLECALCIFEROL, ALFACALCIDOL**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Alfacalcidol: No Cholecalciferol: Yes
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	E20.9
Drug Class	Vitamin D Analog
Drug Sub-class	
ATC Code	**A11CC03** **A11CC05**
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Oral drops, solution Capsule Injection Film-coated tablet
Route of Administration	Oral use Intravenous use
Dose (Adult) [DDD]*	**Alfacalcidol:** **Hypoparathyroidism, chronic (off-label use): Oral:** Initial (low end of range): 0.5 mcg/day; may adjust dose carefully in increments of 0.25 to 0.5 mcg/day not more frequently than every 2 to 3 days to achieve desired calcium levels while avoiding hypercalcemia. Usual range: 0.5 to 4 mcg/day **Cholecalciferol:** **Oral: Initial dosing:**

	High-dose therapy: May be preferred in patients with a serum 25(OH)D level <12 ng/mL (<30 nmol/L) or who are symptomatic, or in patients with concomitant hypocalcemia. **Oral**: 50,000 units (1,250 mcg) once weekly (or equivalent dose administered once daily) for 6 to 12 weeks, then recheck 25(OH)D level; may repeat high-dose therapy if needed to achieve target 25(OH)D level. **Low-dose therapy**: May be preferred in patients with a serum 25(OH)D level 12 to <20 ng/mL (30 to <50 nmol/L) without symptoms or concomitant hypocalcemia. **Oral**: 800 to 1,000 units (20 to 25 mcg) once daily for ~3 to 4 months; may adjust dose if needed every 3 to 4 months based on 25(OH)D level. Some experts suggest modest dose increases (eg, to 2,000 units [50 mcg] once daily) if serum 25(OH)D levels have substantially increased but remain below target or switching to high-dose therapy if serum 25(OH)D levels remain substantially below target. **Maintenance dosing: Oral:** Once target 25(OH)D level is achieved, continue at a maintenance dose of 600 to 2,000 units (15 to 50 mcg) once daily.
Maximum Daily Dose Adults*	**Alfacalcidol:** 4 mcg/day **Cholecalciferol: High-dose therapy: Oral**: 50,000 units (1,250 mcg) once weekly
Dose (pediatrics)	**Alfacalcidol:** **Neonates and premature infants: IV, Oral: Initial**: 0.05 to 0.1 mcg/kg/day. **Infants and Children <20 kg: IV**, **Oral: Initial:** 0.05 mcg/kg/day. Adjust dose

	according to clinical response using caution to avoid hypercalcemia. **Children and Adolescents ≥20 kg: IV, Oral: Initial**: 1 mcg once daily; if needed, may titrate upward in weekly increments of 0.25 to 0.5 mcg using caution to avoid hypercalcemia. Following initial response, maintenance doses of 0.25 to 1 mcg/day may be sufficient depending on condition being treated. If hypercalcemia occurs, interrupt therapy until plasma calcium returns to normal, then restart at a reduced dose (eg, 50% of previous dose). **Cholecalciferol: Oral:** **Infants: Oral**: 2,000 units (50 mcg) daily for 6 weeks to achieve a serum 25(OH)D level >20 ng/mL; followed by a maintenance dose of 400 to 1,000 units (10 to 25 mcg) daily. **Children and Adolescents: Oral:** 2,000 units (50 mcg) daily for 6 to 8 weeks to achieve serum 25(OH)D level >20 ng/mL; followed by a maintenance dose of 600 to 1,000 units (15 to 25 mcg) daily. Note: For patients at high risk of fractures a serum 25(OH)D level >30 ng/mL has been suggested.
Maximum Daily Dose Pediatrics*	**Cholecalciferol: Oral**: 2,000 units (50 mcg) daily
Adjustment	No dosage adjustments provided in hepatic and kidney impairment.
Prescribing edits*	CU
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): To be administered concurrently with calcium supplementation to correct hypocalcemia.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	

QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Alfacalcidol: Frequency not defined:** Cardiac arrhythmia, hypertension, Albuminuria, decreased libido, hypercholesterolemia, polydipsia, weight loss, Asthenia, drowsiness, fatigue, headache, hyperthermia, metallic taste, psychosis, vertigo **Cholecalciferol:** No adverse reactions listed in the manufacturer's labeling.
Drug Interactions*	**Alfacalcidol:** X Burosumab X Calcifediol X Calcipotriene X Calcitriol (Systemic) X Calcitriol (Topical) X Cholecalciferol X Doxercalciferol X Ergocalciferol X Multivitamins/Fluoride (with ADE) Depends on Dose X Multivitamins/Minerals (with ADEK, Folate, Iron) Depends on Dose X Paricalcitol X Tacalcitol D Almagate D Aluminum Hydroxide D Cholestyramine Resin Depends on Route D Colesevelam Depends on Route D Colestipol Depends on Route D Diomagnite D Dolomite D Erdafitinib D Magaldrate

	D Magnesium Aspartate D Magnesium Carbonate D Magnesium Chloride D Magnesium Citrate D Magnesium Glucoheptonate D Magnesium Gluconate D Magnesium Glycerophosphate D Magnesium Hydroxide D Magnesium L-aspartate Hydrochloride D Magnesium L-lactate D Magnesium Oxide D Magnesium Salicylate D Magnesium Sulfate D Magnesium Trisilicate D Mineral Oil Depends on Route D Orlistat Depends on Route D Sucralfate **Cholecalciferol** X Alfacalcidol X Calcifediol X Calcipotriene X Calcitriol (Systemic) X Calcitriol (Topical) X Doxercalciferol X Ergocalciferol X Multivitamins/Fluoride (with ADE) Depends on Dose X Multivitamins/Minerals (with ADEK, Folate, Iron) Depends on Dose X Paricalcitol X Tacalcitol D Cholestyramine Resin Depends on Route D Colesevelam Depends on Route D Colestipol Depends on Route D Erdafitinib D Mineral Oil Depends on Route D Orlistat Depends on Route

Special Population	**Cholecalciferol**: Special populations (eg, obesity, patients on medications known to affect vitamin D metabolism, malabsorption, gastrectomy): Higher doses or longer durations may be necessary for adequate replacement. In patients with malabsorption when target 25(OH)D levels cannot be maintained with cholecalciferol, consider switching to hydroxylated vitamin D metabolites (eg, calcitriol)
Pregnancy	**Alfacalcidol:** Adverse events have been observed in animal reproduction studies. **Cholecalciferol:** The cholecalciferol metabolite, 25(OH)D, crosses the placenta; maternal serum concentrations correlate with fetal concentrations at birth.
Lactation	**Alfacalcidol** may be present in breast milk. Breastfeeding is not recommended by the manufacturer**.** **Cholecalciferol** is present in breast milk. Maternal vitamin D requirements are the same for breastfeeding and nonbreastfeeding females.
Contraindications	Hypersensitivity to 1-α-hydroxyvitamin D3, vitamin D or its analogues and derivatives, or any component of the formulation; hypercalcemia; hyperphosphatemia; evidence of vitamin D toxicity
Monitoring Requirements	Serum calcium, phosphate, and magnesium; renal function [ie, 24-hour urinary calcium and creatinine, blood urea nitrogen (BUN), measured creatinine clearance or estimated glomerular filtration rate (eGFR)]; renal imaging (every 5 years in asymptomatic patients with a history of renal lithiasis or calcinosis or more frequently as

	indicated); CNS imaging (basal ganglia and other sites of calcification), ophthalmologic exam, and/or BMD as clinically indicated. Signs and symptoms of vitamin D toxicity (eg hypercalcemia, hypercalcuria, confusion, psychosis, tremor, calcification of soft tissues, nausea, weakness).
Precautions	**Concerns related to adverse effects:** • Excessive vitamin D: Excessive vitamin D administration may lead to over suppression of parathyroid hormone (PTH), progressive or acute hypercalcemia, hypercalciuria, hyperphosphatemia, and adynamic bone disease. • Hypercalcemia: Monitor calcium levels closely; patients with chronic renal failure are at an increased risk for hypercalcemia. Dose reduction or discontinuation of therapy may be necessary. Withhold calcium supplementation until calcium levels normalize. Discontinue use with hypercalcemia in dialysis patients; may reinstitute therapy at 50% of previous dose 1 week after calcium levels have normalized. Chronic hypercalcemia may result in generalized vascular and soft tissue calcification, exacerbate nephrolithiasis, and has been associated with increased mortality in adults with chronic kidney disease (CKD). • Hyperphosphatemia: Monitor serum phosphate; in cases of progressively or persistently elevated serum phosphate, the use of phosphate-lowering agents may be necessary.

	Disease-related concerns: • Cardiovascular: Avoid prolonged hypercalcemia; may aggravate arteriosclerosis or cardiac valve sclerosis. Use with caution in patients with calcification of pulmonary tissue; may result in cardiac disease. Severe hypercalcemia may increase risk of cardiac arrhythmias. • Granulomatous diseases: Use with caution in patients with granulomatous diseases (eg, sarcoidosis) due to increased sensitivity to vitamin D. **Dosage form specific issues:** • Ethanol: Oral drops/injection [International labeling]: Some dosage forms contain ethanol; use with caution in patients with a history of alcoholism, women who are pregnant or breastfeeding, pediatrics, or high-risk groups such as liver disease or epilepsy. • Propylene glycol: IV [International labeling]: Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures and respiratory depression; use caution. See manufacturer's labeling. • Sesame oil: Capsule [International labeling]: Some dosage forms contain sesame oil; may cause severe allergic reactions. • Sorbitol: Oral drops [International labeling]: Some dosage forms may contain sorbitol; avoid use in patients with hereditary fructose intolerance.
Black Box Warning	N/A

REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hypoparathyroidism treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Vitamin D.**

Table 21. Vitamin D HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Vitamin D	NICE	No recommendations for this indication.
	CADTH	No recommendations for this indication.
	HAS	No recommendations for this indication.
	IQWIG	No recommendations for this indication.
	PBAC	No recommendations for this indication.

CONCLUSION STATEMENT – Vitamin D

Vitamin D supplementation is part of the standard therapy for the management of hypoparathyroidism. While there are no recommendations by major HTA bodies for the use of vitamin D in hypoPT, the various vitamin D have been available on the market for years and mostly marketed as over the counter (OTC) drugs, leading to a relatively low cost of treatment.

2.3 Magnesium Supplement

Table 22. Magnesium Drug Information

SCIENTIFIC NAME **Magnesium**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E20.9
Drug Class	Electrolyte Supplement, Magnesium Salt
Drug Sub-class	
ATC Code	A06AD19 A02AA04 A12CC02
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Effervescent powder Suspension Solution for injection
Route of Administration	Oral use Parenteral use
Dose (Adult) [DDD]*	**Magnesium Sulfate:** **Asymptomatic patients:** Note: Oral replacement using a different salt (eg, magnesium chloride) is generally preferred if tolerated. Slow IV administration (≤1 g/hour) may provide more efficient repletion due to potential for rapid urinary elimination. **Initial:** **Mild deficiency** (eg, serum magnesium >1.5 to 1.9 mg/dL): IV: 1 to 2 g over 1 to 2 hours.

	Moderate deficiency (eg, serum magnesium 1 to 1.5 mg/dL): IV: 2 to 4 g over 2 to 12 hours. **Severe deficiency** (eg, serum magnesium <1 mg/dL): IV: 4 to 8 g over 4 to 24 hours **Symptomatic patients (eg, tetany, arrhythmias, seizures) (excluding torsades de pointes and eclampsia/preeclampsia):** Note: Continuous cardiac monitoring strongly recommended. Subsequent dosing may be based on serum magnesium levels assessed 6 to 12 hours after initial dosing. Repletion may take several days. IV: Hemodynamically unstable: Initial: 1 to 2 g administered as a bolus over 2 to 15 minutes; may repeat as needed if patient remains unstable; once patient is stable, administer an additional 4 to 8 g over 12 to 24 hours. Hemodynamically stable: Initial: 1 to 2 g over 5 to 60 minutes, followed by an additional 4 to 8 g over 12 to 24 hours.
Maximum Daily Dose Adults*	**IV magnesium sulfate:** 8 g over 4 to 24 hours
Dose (pediatrics)	**Dose expressed as magnesium sulfate: IV, Intraosseous:** 25 to 50 mg /kg/dose every 6 hours for 2 to 3 doses, then recheck serum concentration; maximum dose: 2,000 mg/dose. **Dose expressed as elemental magnesium: IV:** 2.5 to 5 mg/kg/dose every 6 hours for 2 to 3 doses. **Oral**: All doses should be followed by 8 ounces of water in patients ≥2 years of age
Maximum Daily Dose Pediatrics*	**Elemental magnesium:** 5 mg/kg/dose every 6 hours for 2 to 3 doses

	Magnesium Sulfate: maximum dose: 2,000 mg/dose
Adjustment	**Hypomagnesemia:** There are no dosage adjustments for renal impairment; however, patients in severe kidney failure should not receive magnesium due to toxicity from accumulation. Patients with a CrCl <30 mL/minute should be monitored by serum magnesium levels. There are no dosage adjustment recommendations for hepatic impairment.
Prescribing edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Frequency not defined:** Cardiovascular: Flushing (IV; dose related), hypotension (IV; rate related), vasodilation (IV; rate related) Hypermagnesemia
Drug Interactions*	**From the monograph of magnesium sulfate:** X Baloxavir Marboxil Depends on Route X Calcium Polystyrene Sulfonate X Levonadifloxacin Depends on Route X Raltegravir Depends on Route X Sodium Polystyrene Sulfonate X Unithiol Depends on Route D Alendronate Depends on Route

	D Alfacalcidol D Alpha-Lipoic Acid Depends on Route D Bictegravir Depends on Route D Cabotegravir Depends on Route D Calcitriol (Systemic) D Ciprofloxacin (Systemic) Depends on Route D Clodronate Depends on Route D Deferiprone Depends on Route D Delafloxacin Depends on Route D Demeclocycline Depends on Route D Dolutegravir Depends on Route D Doxercalciferol D Doxycycline Depends on Route D Eltrombopag Depends on Route D Elvitegravir Depends on Route D Enoxacin Depends on Route D Etidronate Depends on Route D Gabapentin Depends on Route D Gemifloxacin Depends on Route D Ibandronate Depends on Route D LevoFLOXacin (Systemic) Depends on Route D Levothyroxine Depends on Route D Lomefloxacin Depends on Route D Lymecycline Depends on Route D Minocycline (Systemic) Depends on Route D Moxifloxacin (Systemic) Depends on Route D Multivitamins/Fluoride (with ADE) D Nalidixic Acid Depends on Route D Norfloxacin Depends on Route D Ofloxacin (Systemic) Depends on Route D Omadacycline Depends on Route D Oxytetracycline Depends on Route D Pefloxacin Depends on Route D PenicillAMINE Depends on Route

	D Pipemidic Acid Depends on Route D Potassium Phosphate Depends on Route D Prulifloxacin Depends on Route D Risedronate Depends on Route D Roxadustat Depends on Route D Sarecycline Depends on Route D Sodium Phosphates Depends on Route D Sparfloxacin Depends on Route D Tetracycline (Systemic) Depends on Route D Tiludronate Depends on Route D Trientine Depends on Route D Zabofloxacin Depends on Route
Special Population	Elderly, due to disease or drug therapy, may be predisposed to diarrhea. Diarrhea may result in electrolyte imbalance. Decreased renal function (CrCl <30 mL/minute) may result in toxicity; monitor for toxicity. Obstetrics: Vigilant monitoring and safe administration techniques are recommended to avoid potential for errors resulting in toxicity. Monitor mother and fetus closely. Use longer than 5 to 7 days may cause adverse fetal events.
Pregnancy	Magnesium crosses the placenta; serum concentrations in the fetus are similar to those in the mother.
Lactation	Magnesium is present in breast milk. Magnesium requirements are the same in breastfeeding and non-breastfeeding females. Although the manufacturer recommends that caution be used if administered to breastfeeding females.
Contraindications	Hypersensitivity to any component of the formulation; heart block; myocardial damage; IV use for

	preeclampsia/eclampsia during the 2 hours prior to delivery. Although the manufacturers' labeling for some IV formulations state use in preeclampsia/eclampsia during the 2 hours prior to (cesarean) delivery is contraindicated due to interaction with neuromuscular-blocking agents intraoperatively; stopping magnesium sulfate prior to cesarean delivery in these patients is not recommended and increases the risk of seizure. Instead, magnesium should be continued prior to and during the delivery. Additionally, the manufacturers' labeling for some IV formulations contraindicates the use of magnesium sulfate in the setting of heart block; however, the use of magnesium is appropriate in patients with serious conditions requiring magnesium therapy who either have mild degrees of heart block (eg, first degree) or more severe forms of heart block with a temporary or permanent cardiac pacemaker.
Monitoring Requirements	IV: Rapid administration: ECG monitoring, vital signs, deep tendon reflexes; magnesium concentrations if frequent or prolonged dosing required particularly in patients with renal dysfunction, calcium, and potassium concentrations; renal function. Obstetrics: Patient status including vital signs, oxygen saturation, respiration, deep tendon reflexes, level of consciousness, fetal heart rate, maternal uterine activity, renal function. Monitor magnesium concentrations every 4 hours in patients with renal dysfunction (every 2 hours if serum magnesium is >8 mEq/L)

Precautions	**Disease-related concerns:** • Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease. • Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication. **Dosage form specific issues:** • Aluminum: The parenteral product may contain aluminum; toxic aluminum concentrations may be seen with high doses, prolonged use, or renal dysfunction. Premature neonates are at higher risk due to immature renal function and aluminum intake from other parenteral sources. Parenteral aluminum exposure of >4 to 5 mcg/kg/day is associated with CNS and bone toxicity; tissue loading may occur at lower doses. See manufacturer's labeling. **Other warnings/precautions**: • Appropriate use: Unlikely to effectively terminate irregular/polymorphic VT (with normal baseline QT interval) • Electrolyte abnormalities: Concurrent hypokalemia or hypocalcemia can accompany a magnesium deficit. Hypomagnesemia is frequently associated with hypokalemia and requires correction in order to normalize potassium. • Parenteral administration: Magnesium toxicity can lead to fatal cardiovascular arrest and/or respiratory paralysis.

Black Box Warning	N/A
REMS*	N/A

The following table shows the percentage of elemental magnesium found in each magnesium salt:

Table 23. Percentage of Elemental Magnesium Found in Each Magnesium Salt

Type of Magnesium	% of Elemental Magnesium
Magnesium Oxide (MgO)	60.3%
Magnesium Carbonate (MgCO3)	28.8%
Magnesium Sulfate (MgSO4)	9.9%
Magnesium Chloride (MgCl2)	25.4%
Magnesium Hydroxide (Mg(OH)2)	41.2%
Magnesium Citrate	Approximately 11.3%
Magnesium Acetate	Approximately 8.2%
Magnesium Lactate	Approximately 12.1%
Magnesium Gluconate	Approximately 5.1%
Magnesium Aspartate	Approximately 11.8%
Magnesium Malate	Approximately 6.7%
Magnesium Taurate	Approximately 8.9%

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hypoparathyroidism treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Magnesium.**

Table 24. Magnesium HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Magnesium	NICE	No recommendations for this indication.
	CADTH	No recommendations for this indication.
	HAS	No recommendations for this indication.
	IQWIG	No recommendations for this indication.

	PBAC	No recommendations for this indication.

CONCLUSION STATEMENT – Magnesium

Magnesium supplementation is part of the standard therapy for the management of Hypoparathyroidism. While there are no recommendations by major HTA bodies for the use of magnesium in hypoPT, the various magnesium salts have been available on the market for years and mostly marketed as over the counter (OTC) drugs, leading to a relatively low cost of treatment.

2.4 Teriparatide

Table 25. Teriparatide Drug Information

SCIENTIFIC NAME **Teriparatide**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E20.9
Drug Class	Parathyroid Hormone Analog
Drug Sub-class	
ATC Code	**H05AA02**
Pharmacological Class (ASHP)	68:24.08 - Parathyroid Agents
DRUG INFORMATION	
Dosage Form	**Solution for injection** **Solution for injection in cartridge**
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	20 mcg twice daily (based on primary literature)[11–13]
Maximum Daily Dose Adults*	20 mcg twice daily (based on primary literature)[11–13]
Dose (pediatrics)	12.5 mcg twice daily (based on primary literature)[14]
Maximum Daily Dose Pediatrics*	12.5 mcg twice daily (based on primary literature)[14]

Adjustment	There are no dosing adjustments required for hepatic impairment. For renal impairment: • eGFR <30 mL/minute/1.73 m2: Use only in patients at very high risk for fracture and in conjunction with guidance from patient's nephrology team, as osteoporosis can be difficult to distinguish from chronic kidney disease mineral and bone disorder (CKD-MDB); many patients with CKD-MBD will already have elevated parathyroid hormone levels, and teriparatide safety and efficacy data are limited. If treatment is necessary, no dosage adjustment is likely to be necessary. • Hemodialysis, intermittent (thrice weekly): Use should generally be avoided. If treatment is necessary, dose as in eGFR <30 mL/minute/1.73m2. • Peritoneal dialysis: Use should generally be avoided. If treatment is necessary, dose as in eGFR <30 mL/minute/1.73m2
Prescribing edits*	MD, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by an endocrinologist.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Assess serum calcium prior to initiation; avoid use in patients with preexisting hypercalcemia or hypercalcemic disorder. Correct vitamin D deficiency (eg, to a 25-hydroxyvitamin D level ≥20 ng/mL [≥50 nmol/L]) prior to initiating therapy and ensure adequate calcium and vitamin D intake during therapy; however, use caution to avoid hypercalcemia.	
EU (Emergency Use Only): N/A	

PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** hypercalcemia, nausea **Most serious**: arthralgia, insomnia, dyspnea, angina pectoris, orthostatic hypotension, syncope, hyperuricemia
Drug Interactions*	B - Digoxin
Special Population	**Older Adult Considerations** No age-related differences in pharmacokinetics have been seen. In studies, no significant difference was seen in either efficacy or adverse effects between older patients and younger patients. Teriparatide should be considered an alternative in patients who cannot tolerate or have not responded to other treatments for osteoporosis.
Pregnancy	Adverse events were observed in animal reproduction studies; consider discontinuing treatment once pregnancy is recognized.
Lactation	It is not known if teriparatide is present in breast milk. The manufacturer recommends avoiding use in patients who are breastfeeding.
Contraindications	Hypersensitivity (eg, anaphylaxis, angioedema) to teriparatide or any component of the formulation. Canadian labeling: Additional contraindications (not in US labeling): Preexisting hypercalcemia; severe renal impairment; metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget disease of the bone); unexplained elevations of alkaline phosphatase; prior external beam or implant radiation therapy involving the skeleton; bone metastases or history of skeletal

	malignancies; pregnancy; breastfeeding; pediatric patients or young adults with open epiphysis.
Monitoring Requirements	Orthostatic hypotension; serum calcium (draw at least 16 hours after teriparatide dose); urinary calcium (patients with suspected active urolithiasis or preexisting hypercalciuria).
Precautions	**Concerns related to adverse effects:** • Cutaneous calcification: Serious worsening of previous stable cutaneous calcification or calciphylaxis has been reported; discontinue use if occurs. Patients with underlying autoimmune disease, kidney failure, or concomitantly taking warfarin or systemic corticosteroids are at increased risk. • Orthostatic hypotension: May cause orthostatic hypotension. Transient orthostatic hypotension usually occurs within 4 hours of dosing and within the first several doses; usually resolved without treatment within a few minutes to a few hours. **Disease-related concerns:** • Hypercalcemia: Use with caution in patients with hypercalcemia (not studied); may increase or exacerbate hypercalcemia. Avoid use in patients with a known history of hypercalcemia disorder (eg, primary hyperparathyroidism). • Urolithiasis: Use with caution in patients with active or recent urolithiasis because of the risk of exacerbation. **Dosage form specific issues:** • Multiple-dose injection pens: According to the Centers for Disease

	Control and Prevention, pen-shaped injection devices should never be used for more than one person (even when the needle is changed) because of the risk of infection. The injection device should be clearly labeled with individual patient information to ensure that the correct pen is used
Black Box Warning	Potential risk of osteosarcoma (generic [620 mcg/2.48 mL] only)
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hypoparathyroidism treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Teriparatide.**

Table 26. Teriparatide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Teriparatide	NICE	No recommendations for this indication.
	CADTH	No recommendations for this indication.
	HAS	No recommendations for this indication.
	IQWIG	No recommendations for this indication.
	PBAC	No recommendations for this indication.

CONCLUSION STATEMENT – Teriparatide

There are no HTA recommendations for the use of teriparatide in hypoparathyroidism. Data for dosing in pediatric patients is scarce. There are few studies in limited number of patients. It is not a labeled indication and there is not much data on its use. It is not routinely used for this indication. No randomized control trials were found, most data are found from case reports.

2.5 Hydrochlorothiazide

Table 27. Hydrochlorothiazide Drug Information

SCIENTIFIC NAME **Hydrochlorothiazide**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E20.9
Drug Class	Antihypertensive; Diuretic, Thiazide
Drug Sub-class	
ATC Code	**C03AA03**
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	**Oral: Initial:** 25 mg once daily; titrate based on tolerance and urinary calcium levels to usual effective dose **Older Adult:** Oral: Initial: 12.5 mg once daily; titrate as necessary in increments of 12.5 mg. Minimal increase in response and more electrolyte disturbances are seen with doses >50 mg daily
Maximum Daily Dose Adults*	100 mg/day in 1 to 2 divided doses
Dose (pediatrics)	Limited data available: Oral: Initial: 1 to 2 mg/kg/day in 1 to 2 divided doses; lower initial doses of 0.5 mg/kg/day has been reported in infants and children; titrate until goal urinary calcium excretion goals reached and symptoms resolve; treatment usually continued for 1 year; usual adult dose: 25 to 100 mg/day
Maximum Daily Dose Pediatrics*	100 mg/day (adults)

Adjustment	**Impaired renal function:** GFR <30 mL/minute/1.73 m2, hemodialysis, peritoneal dialysis: Use not recommended; use is contraindicated with anuria. **Impaired hepatic function:** use with caution and monitor for precipitation of hepatic coma, no recommended dose adjustments.
Prescribing edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Dermatologic toxicity Electrolyte disturbances Gout Hypersensitivity reactions (immediate and delayed) Ocular Effects
Drug Interactions*	X Aminolevulinic Acid (Systemic) X Bromperidol X Dofetilide X Levosulpiride X Promazine D Amifostine D Arsenic Trioxide D Cholestyramine Resin Depends on Route D Colesevelam Depends on Route D Colestipol Depends on Route

	D Lithium Depends on International labeling D Mecamylamine D Obinutuzumab
Special Population	Beers Criteria: Diuretics are identified in the Beers Criteria as potentially inappropriate medications to be used with caution in patients 65 years and older due to the potential to cause or exacerbate syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatremia; monitor sodium concentration closely when initiating or adjusting the dose in older adults.
Pregnancy	Hydrochlorothiazide crosses the placenta. Maternal use may cause fetal or neonatal jaundice, thrombocytopenia, or other adverse events observed in adults.
Lactation	Hydrochlorothiazide is present in breast milk. Due to the potential for serious adverse reactions in the breastfeeding infant, the manufacturer recommends a decision be made whether to discontinue breastfeeding or to discontinue the drug, considering the importance of treatment to the mother. Hydrochlorothiazide is considered compatible with breastfeeding. However, thiazide diuretics have the potential to decrease milk volume and suppress lactation; use should be avoided when possible.
Contraindications	Hypersensitivity to hydrochlorothiazide, any component of the formulation, or sulfonamide-derived drugs; anuria Note: Although the FDA-approved product labeling states this medication is contraindicated in patients with hypersensitivity to sulfonamide-containing drugs, the scientific basis of

	this cross-sensitivity has been challenged. See “Warnings/Precautions” for more detail. Canadian labeling: Additional contraindications (not in US labeling): Increasing azotemia and oliguria during treatment of severe progressive renal disease; breast-feeding.
Monitoring Requirements	Blood pressure; fluid intake and output; serum electrolytes; BUN, serum creatinine; skin to assess for photosensitivity and skin cancer; visual acuity, ocular pain.
Precautions	**Concerns related to adverse effects**: • Sulfonamide (“sulfa”) allergy: The FDA-approved product labeling for many medications containing a sulfonamide chemical group includes a broad contraindication in patients with a prior allergic reaction to sulfonamides. There is a potential for cross-reactivity between members of a specific class (eg, two antibiotic sulfonamides). However, concerns for cross-reactivity have previously extended to all compounds containing the sulfonamide structure (SO2NH2). An expanded understanding of allergic mechanisms indicates cross-reactivity between antibiotic sulfonamides and nonantibiotic sulfonamides may not occur or at the very least this potential is extremely low. In particular, mechanisms of cross-reaction due to antibody production (anaphylaxis) are unlikely to occur with nonantibiotic sulfonamides. T-cell-mediated (type IV) reactions (eg, maculopapular rash) are less well understood and it is not possible to completely exclude this potential based on current insights. In

	cases where prior reactions were severe (Stevens-Johnson syndrome/TEN), some clinicians choose to avoid exposure to these classes. **Disease-related concerns:** • Adrenal insufficiency: Avoid use of diuretics for treatment of elevated blood pressure in patients with primary adrenal insufficiency (Addison disease). Adjustment of glucocorticoid/mineralocorticoid therapy and/or use of other antihypertensive agents is preferred to treat hypertension • Ascites due to cirrhosis: Use with extreme caution or avoid hydrochlorothiazide in the management of ascites due to cirrhosis; may lead to rapid development of hyponatremia when used in combination with spironolactone and furosemide. • Bariatric surgery: Dehydration: Avoid diuretics in the immediate postoperative period after bariatric surgery; electrolyte disturbances and dehydration may occur. Diuretics may be resumed, if indicated, once oral fluid intake goals are met • Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control. • Hepatic impairment: Use with caution in patients with severe hepatic dysfunction; in progressive or severe liver disease, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy/coma. • Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations;

	increased cholesterol and triglyceride levels have been reported. • Parathyroid disease: Thiazide diuretics reduce calcium excretion; pathologic changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed with prolonged use; should be discontinued prior to testing for parathyroid function. • Renal impairment: Cumulative effects may develop, including azotemia, in patients with impaired renal function. Avoid in severe renal disease (ineffective). • Systemic lupus erythematosus (SLE): May cause SLE exacerbation or activation. **Special populations**: • Surgical patients: If given the morning of surgery, hydrochlorothiazide may render the patient volume depleted and blood pressure may be labile during general anesthesia. **Dosage form specific issues**: • Propylene glycol: Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated with hyperosmolality, lactic acidosis, seizures and respiratory depression; use caution. See manufacturer's labeling.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hypoparathyroidism treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency

in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Hydrochlorothiazide.**

Table 28. Hydrochlorothiazide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Hydrochlorothiazide	NICE	No recommendations for this indication.
	CADTH	No recommendations for this indication.
	HAS	No recommendations for this indication.
	IQWIG	No recommendations for this indication.
	PBAC	No recommendations for this indication.

CONCLUSION STATEMENT – Hydrochlorothiazide

While there are no recommendations for the use of hydrochlorothiazide in hypoparathyroidism, it has been available on the market for many years and multiple generic options have been developed, leading to a relatively low cost of treatment. It is typically used to reduce urinary calcium excretion/ for persistent hypercalciuria despite calcium and vitamin D supplementation.

2.6 Sevelamer

Table 29. Sevelamer Drug Information

SCIENTIFIC NAME **Sevelamer**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	E20.9
Drug Class	Phosphate Binder
Drug Sub-class	
ATC Code	**V03AE02**
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Powder for oral suspension Film-coated tablet

Route of Administration	Oral Use
Dose (Adult) [DDD]*	Sevelamer carbonate and sevelamer hydrochloride are dosed the same on a mg-to-mg basis; when switching between products, use the same dose. **Oral: Initial**: Based on serum phosphorous levels: >5.5 to <7.5 mg/dL: 800 mg 3 times daily with meals. 7.5 to <9 mg/dL: 1,200 to 1,600 mg 3 times daily with meals. ≥9 mg/dL: 1,600 mg 3 times daily with meals. Dosage adjustment: Increase or decrease dose by 400 to 800 mg per meal at 2-week intervals as needed to obtain targeted serum phosphorus concentrations; usual dosage range: 800 to 2,400 mg 3 times daily
Maximum Daily Dose Adults*	2,400 mg 3 times daily
Dose (pediatrics)	**Sevelamer carbonate (Renvela):** Children ≥6 years and Adolescents: Patients not taking a phosphate binder: Initial dose: BSA ≥0.75 to <1.2 m2: Oral: 800 mg 3 times daily with meals; titrate as needed by 400 mg per dose at 2-week intervals. BSA ≥1.2 m2: Oral: 1,600 mg 3 times daily with meals; titrate as needed by 800 mg per dose at 2-week intervals. Dosage adjustment when switching from calcium acetate to sevelamer carbonate: 667 mg of calcium acetate is equivalent to ~800 mg of sevelamer; conversion based on dose per meal: Calcium acetate 667 mg: Convert to 800 mg sevelamer carbonate. Calcium acetate 1,334 mg: Convert to 1,600 mg sevelamer carbonate.

	Calcium acetate 2,001 mg: Convert to 2,400 mg sevelamer carbonate. **Sevelamer hydrochloride (Renagel):** Infants ≥10 months and Children <2 years: Very limited data: Oral: Mean final dose of 140 ± 86 mg/kg/day (5.38 ± 3.24 g/day) was reported in a small trial (n=18; age range: 10 months to 18 years) to achieve the targeted serum phosphorus level. Initial dosing was based upon prior phosphate binder dose and serum phosphorus concentrations. In a case report of a 19-month-old, an initial dose of 100 mg/kg/day divided every 8 hours with titration up to 130 mg/kg/day was reported to effectively lower serum phosphorus levels. Children ≥2 years and Adolescents: Limited data available: Oral: Initial dose: 400 or 800 mg 3 times daily administered with meals; titrate at monthly intervals in 1,200 mg/day increments (ie, 400 mg at each meal) to target phosphorus level; final mean range: 140 to 163 mg/kg/day (5.38 to 6.7 g/day); dosing based on experience in 46 patients; prior or final comparative calcium salt phosphate-binder dose: 4 ± 3 g/day. Dosage adjustment when switching from calcium acetate to sevelamer hydrochloride: 667 mg of calcium acetate is equivalent to ~800 mg of sevelamer; conversion based on dose per meal.
Maximum Daily Dose Pediatrics*	5.38 to 6.7 g/day
Adjustment	No dosage adjustments for hepatic or renal impairment.
Prescribing edits*	AGE

AGE (Age Edit): Sevelamer carbonate: Use in Children ≥6 years. Sevelamer hydrochloride: Use in Infants ≥10 months	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** metabolic acidosis, diarrhea, dyspepsia, nausea, vomiting. **Most serious:** peritonitis, colitis, gastrointestinal necrosis, intestinal perforation.
Drug Interactions*	D Cholic Acid D Ciprofloxacin (Systemic) Depends on Route D Levothyroxine D Mycophenolate D Roxadustat
Special Population	Since electrolyte changes (ie, phosphorus, calcium) can have dramatic effects in the elderly, monitor closely.
Pregnancy	Sevelamer is not absorbed systemically; however, it may reduce maternal absorption of fat-soluble vitamins and folic acid; supplementation may be needed.
Lactation	Sevelamer is not absorbed systemically, and breastfeeding is not expected to cause exposure to a breastfeeding infant. Sevelamer may reduce maternal absorption of fat-soluble vitamins and folic acid; supplementation may be needed.

Contraindications	Hypersensitivity to sevelamer or any component of the formulation; bowel obstruction Canadian labeling: Additional contraindications (not in US labeling): Hypophosphatemia; active mucosal injury (eg, necrosis, perforation, ulcerative colitis, GI bleeding)
Monitoring Requirements	Serum chemistry, including bicarbonate and chloride. Serum calcium, phosphorus, and parathyroid hormone (PTH): Frequency of measurement may be dependent upon the presence and magnitude of abnormalities, the rate of progression of chronic kidney disease (CKD), and the use of treatments for chronic kidney disease-mineral and bone disorder: CKD stage G3a to G3b: Serum calcium and phosphate: Every 6 to 12 months; PTH: Frequency based on baseline level and progression of CKD CKD stage G4: Serum calcium and phosphate: Every 3 to 6 months; PTH: Every 6 to 12 months CKD stage G5 and G5D: Serum calcium and phosphate: Every 1 to 3 months; PTH: Every 3 to 6 months Periodic 24-hour urinary calcium and phosphorus; magnesium; alkaline phosphatase every 12 months or more frequently in the presence of elevated PTH; creatinine, BUN, albumin; intact parathyroid hormone (iPTH) every 3 to 12 months depending on CKD severity
Precautions	**Concerns related to adverse effects:** • GI effects: Bowel obstruction, bleeding GI ulcers, colitis, ulceration, necrosis, and perforation have been reported; consider discontinuation of therapy in patients who develop severe symptoms.

	Dysphagia and esophageal tablet retention have also been reported with the tablet formulation; consider change to suspension formulation in patients with a history of swallowing disorders. **Disease-related concerns:** • Gastrointestinal disease: Use with caution in patients with gastrointestinal disorders including dysphagia, swallowing disorders, severe gastrointestinal motility disorders (including severe constipation), or major gastrointestinal surgery. **Concurrent drug therapy issues:** • Vitamins: May cause reductions in vitamin D, E, K, or folic acid absorption. **Dosage form specific issues:** • Tablets: Should not be taken apart or chewed; broken or crushed tablets will rapidly expand in water/saliva and may be a choking hazard.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hypoparathyroidism treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Sevelamer.**

Table 30. Sevelamer HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Sevelamer	NICE	No recommendation for this indication.
	CADTH	No recommendation for this indication.
	HAS	No recommendation for this indication.
	IQWIG	No recommendation for this indication.
	PBAC	No recommendation for this indication.

CONCLUSION STATEMENT – Sevelamer

There are no HTA recommendations for the use of sevelamer in hypoparathyroidism. It is typically used to reduce urinary calcium excretion/ for persistent hypercalciuria despite calcium and vitamin D supplementation.

2.7 Other Drugs

This section details drugs that have been approved by the FDA and/or EMA, but are not currently registered by the SFDA.

2.7.1 Natpara® (Parathyroid Hormone) (PTH 1-84)

Natpara® is a medication used to treat hypocalcemia in patients with hypoparathyroidism when calcium supplements and active vitamin D alone are insufficient. It is administered via subcutaneous injection, with dosing based on serum calcium levels. Natpara® raises serum calcium levels by increasing calcium reabsorption in the kidneys, enhancing intestinal calcium absorption, and promoting bone turnover.

The FDA approved Natpara® in January 2015 based on a study in which patients with hypoparathyroidism were randomized to receive Natpara® or a placebo. Natpara® significantly improved calcium control, reducing the need for active vitamin D and oral calcium supplements. However, Natpara® carries a black box warning due to the potential risk of osteosarcoma and is only available through a risk evaluation and mitigation strategy (REMS) program.

Section 3.0 Key Recommendations Synthesis

- Acute management of symptomatic hypocalcemia includes intravenous calcium gluconate (N/A, Management of Hypoparathyroidism, 2016 [8])
- **Chronic Hypoparathyroidism Management:**
    - Primary therapy involves using activated vitamin D analogues along with calcium supplements in divided doses (Very low quality of evidence) (European Society of Endocrinology, 2015[5])
    - Consider reducing calcium intake, implementing a sodium-restricted diet, and/or using a thiazide diuretic in patients with hypercalciuria (Very low quality of evidence) (European Society of Endocrinology, 2015[5])
    - Traditional therapy involves careful use of calcium and active vitamin D (calcitriol or analogs), as well as parent Vitamin D (cholecalciferol or ergocalciferol) (N/A, Management of Hypoparathyroidism, 2016[8])
    - Calcium carbonate is commonly used for supplementation (N/A, Management of Hypoparathyroidism, 2016[8])
    - Routine replacement therapy with PTH or PTH analogues is not recommended (Very low quality of evidence) (European Society of Endocrinology, 2015[5]).
    - Thiazide diuretics can help in cases of hypercalciuria (N/A, Management of Hypoparathyroidism, 2016[8])
    - Phosphate binders or low-phosphate diets are recommended only for severe hyperphosphatemia (above 6.5 mg/dL) (N/A, Management of Hypoparathyroidism, 2016[8])
    - Active vitamin D (1,25-dihydroxyvitamin D; calcitriol) compensates for impaired renal conversion in hypoparathyroidism. Other vitamin D formulations that undergo activation in the liver are used such as 1α-hydroxyvitamin D (alfacalcidol) (N/A, Management of Hypoparathyroidism, 2016[8])
    - Titrating upward the use of active vitamin D formulations can help to reduce the amount of calcium supplementation patients require (N/A, Management of Hypoparathyroidism, 2016[8])
    - Parental vitamin D forms (vitamin D3 [cholecalciferol]) are also used (N/A, Management of Hypoparathyroidism, 2016[8])
    - Monitor serum potassium and magnesium to prevent hypokalemia or hypomagnesemia (N/A, Management of Hypoparathyroidism, 2016[8])

    - PTH (1-34) and PTH (1-84) have shown promise in controlling symptoms and reducing calcium and active vitamin D needs (N/A, Management of Hypoparathyroidism, 2016[8]).
- **Preoperative Vitamin D Deficiency:**
    - It may be appropriate to initiate scheduled oral calcium supplementation and Correction of vitamin D deficiency preoperatively (N/A, American Thyroid Association, 2018[6]).
    - Prophylactic postoperative management often involves prescribing oral calcium and calcitriol without testing PTH or calcium levels, which can help reduce postoperative hypocalcemia (N/A, American Thyroid Association, 2018[6]).
- **Treatment of Progressive/Symptomatic Hypoparathyroidism**
    - If severe hypocalcemia develops despite oral calcium and calcitriol therapy, perform a 12-lead EKG, measure the corrected QT interval, and administer IV calcium (N/A, American Thyroid Association, 2018[6]).
    - Thiazide diuretics can be considered if calcium control remains difficult: If no contraindications exist, hydrochlorothiazide 12.5–50 mg daily may be effective, but it must be titrated to avoid hypotension (N/A, American Thyroid Association, 2018[6]).
- Avoid hyperphosphatemia by administering calcium supplements with meals to act as phosphate binders, implementing a low-phosphate diet in adults if necessary, and using active vitamin D analogue therapy judiciously. Currently, there is no evidence of hyperphosphatemia causing ectopic calcification in HypoPT (N/A, Second International Workshop, 2022[9]).
- Ensure that plasma magnesium levels are normalized and provide magnesium supplements as tolerated by the patient (N/A, Second International Workshop, 2022[9])
- PTH replacement therapy should be considered for patients who are not adequately controlled with conventional therapy, which includes symptomatic hypocalcemia, hyperphosphatemia, renal insufficiency, hypercalciuria, or poor quality of life. Patients requiring high doses of conventional therapy (i.e., calcium >2 g/day or active vitamin D > 2 mcg/day) may also find PTH therapy beneficial (N/A, Second International Workshop, 2022[9])
- Avoid the use of thiazide diuretics and PTH or PTH analogues during pregnancy (N/A, Second International Workshop, 2022[9])

- Severe, sudden-onset low levels of calcium in the body are managed by administering calcium through intravenous injections. This is followed by a continuous drip of calcium, along with the addition of oral calcium supplements and active vitamin D. It's also important to address any existing magnesium deficiency. Quality of evidence: low (standard practice) (Canadian and International Consensus, 2019[4])
- To decrease the amount of calcium excreted in urine, opt for a low-sodium diet and, if possible, think about using hydrochlorothiazide, chlorthalidone, or indapamide. If there are kidney-related issues, you might also want to contemplate the use of rhPTH(1–84). Quality of evidence: low. (Canadian and International Consensus, 2019[4])
- The option of rhPTH(1–84) replacement therapy can be contemplated when serum calcium levels are challenging to regulate, substantial amounts of calcium or active vitamin D are needed, renal issues are evident, quality of life is subpar, or there is gastrointestinal malabsorption. Quality of evidence: low. (Canadian and International Consensus, 2019[4])

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of hypoparathyroidism.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

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11. Efficacy of Teriparatide in Patients with Hypoparathyroidism: A Prospective, Open-label Study.
12. Long term treatment with teriparatide in hypoparathyroidism.
13. Teriparatide Therapy and Reduced Postoperative Hospitalization for Postsurgical Hypoparathyroidism.
14. Teriparatide (rhPTH 1-34) treatment in the pediatric age: long-term efficacy and safety data in a cohort with genetic hypoparathyroidism.

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

II. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose. If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

III. What information is available in the notes?

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

IV. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

V. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

VI. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Description

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. MeSH Terms PubMed

The following is the result of the PubMed search conducted for guideline search:

Query	Filters	Search Details	Results
((Hypoparathyroidism[MeSH Terms]) OR (Idiopathic Hypoparathyroidism[Title/Abstract])) OR (Hypoparathyroidism, Idiopathic[Title/Abstract])	Guideline, in the last 5 years, English	("Hypoparathyroidism"[MeSH Terms] OR "idiopathic hypoparathyroidism"[Title/Abstract] OR (("Hypoparathyroidism"[MeSH Terms] OR "Hypoparathyroidism"[All Fields] OR "hypoparathyroid"[All Fields] OR "hypoparathyroidisms"[All Fields]) AND "Idiopathic"[Title/Abstract])) AND ((y_5[Filter]) AND (guideline[Filter]) AND (english[Filter]))	3

Appendix D. Treatment Algorithm

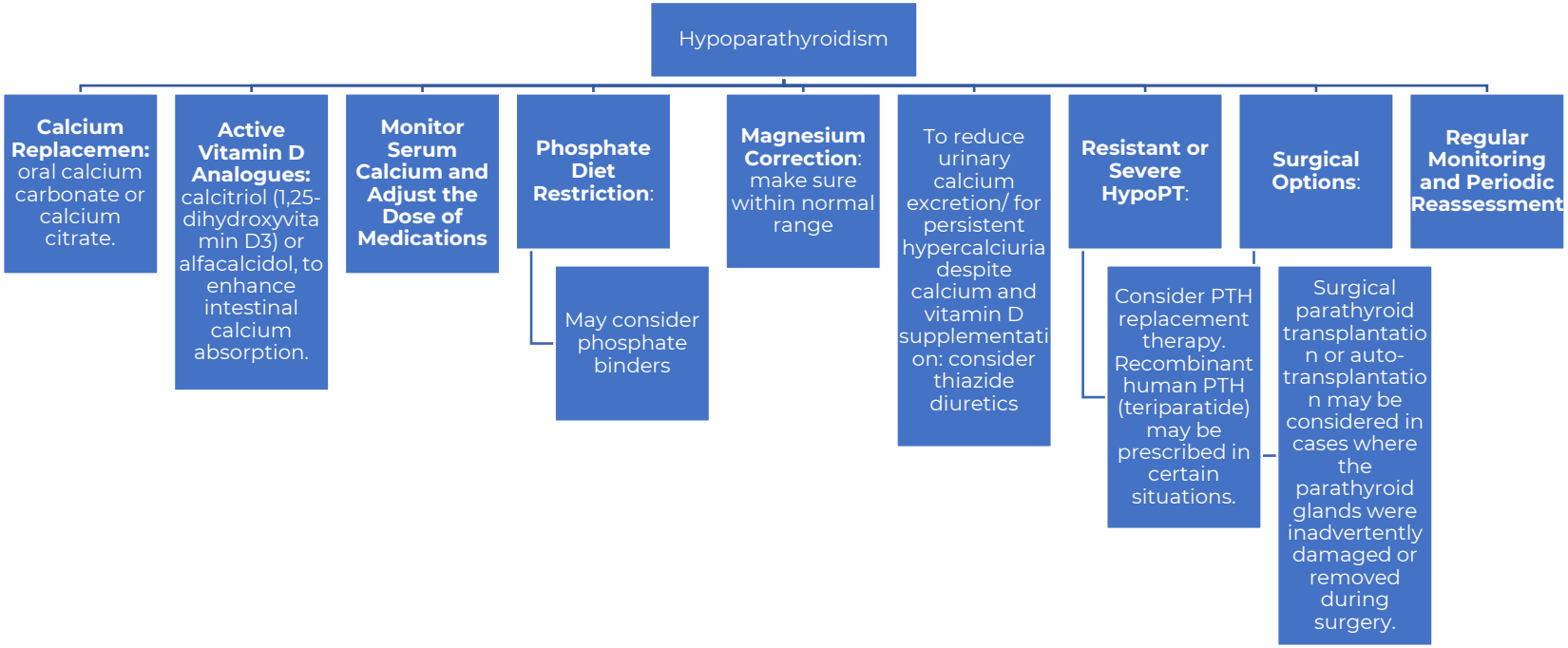

Figure 1. *Treatment Algorithm for the Management of Hypoparathyroidism*